PATTERN OF CHANGES IN THE MR PERFUSION PARAMETERS AND DEVELOPMENT OF NEW DWI LESIONS IN SYMPTOMATIC CASES OF CAROTID STENOSIS FOLLOWING CAROTID STENTING: A PROSPECTIVE STUDY

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DECLARATION

I, **Dr. Arvinda HR** hereby declare that I have actually carried out the project "**Pattern Of Changes In The MR Perfusion Parameters And Development Of New DWI Lesions In Symptomatic Cases Of Carotid Stenosis Following Carotid Stenting: A Prospective Study**" independently under supervision and guidance in this institute.

Date – Sep 2008.

Trivandrum.

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CERTIFICATE

This is to certify that the work contained in this thesis have been carried out by **Dr. Arvinda HR** in the Department of Imaging Sciences and Interventional Radiology, Sree Chitra Tirunal Institute of Medical Sciences and Technology ,Trivandrum ,during his rotatory postings as per schedule, under my guidance and is to my satisfaction.

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Introduction

INTRODUCTION

Stroke (brain attack) represents one of the most serious causes of mortality and morbidity throughout the world. Morbidity due to stroke is a major concern throughout the world due to its economic implication on family, society and country. Each year, 150,000 patients die as a direct result of a cerebrovascular accident (CVA), while 600,000 patients experience the morbidity of aphasia, blindness, or paralysis. In United States, among patients with stroke, internal carotid artery (ICA) stenosis appears to be the most frequent cause (1, 2). The mechanisms of ischemia are essentially two: hemodynamic, for cerebral hypoperfusion, and embolic, due to distal mobilization of atheromatous or thrombocythemic material, almost always secondary to plaque ulceration (3).

Interventional procedures aimed at reducing the risk of stroke in patients with severe stenosis of the internal carotid arteries (ICAs) include surgical endarterectomy (4, 5), percutaneous transluminal angioplasty (PTA) (6) and a combination of angioplasty with endovascular stent insertion (7). With the improvement in the microcatheter, microguidewire and stent technology carotid artery stent placement has emerged as a potential alternative for carotid endarterectomy (8-10). Whether the reductions in stroke risk afforded by these interventional procedures wholly result from a reduced embolism rate, from improved cerebral blood flow, or from a combination of the two remains unproven (11).

The major risk of CAS appears to be the possibility of periprocedural embolic strokes due to release of debris during endovascular manipulation and subsequent distal embolization of solid material into the cerebral circulation (12, 13).

Cerebral protection devices are developed and are currently used widespread in the CAS procedure to limit cerebral embolism secondary to plaque fragments mobilization (14). The role of cerebral protection during the endovascular procedure of revascularization is still under study and clinical investigation, but it is feasible, effective, and seems to reduce the procedural neurological event rate (15).

It has been found that the incidence of major and minor strokes are significantly reduced if the CAS procedure is made with a cerebral protection device with respect to unprotected procedures (16), and therefore, protected CAS seems to decrease thromboembolic complications. Moreover, in high-surgical risk patients, protected CAS was not inferior to CEA in reducing the cumulative incidence of major cardiovascular events within 1 year (17).

Diffusion-weighted MRI (DWI) is sensitive to early brain ischemia and is widely available, and can be used to assess the safety and efficacy of neurovascular intervention (18,19). Based on the lesion pattern, DWI findings after endovascular diagnostic and interventional procedures are supposed to indicate the occurrence of cerebral microemboli that are usually asymptomatic and named silent cerebral ischemia (20).

Stent implantation in the carotid artery is associated with new areas of cerebral ischemia, detected by using diffusion-weighted magnetic resonance images during both the protected and unprotected endovascular procedures (12, 21).

When perfusion pressure decreases secondary to proximal stenosis, functional compensation mechanisms activate cerebral autoregulation, avoiding, within certain limits, the manifestation of ischemic lesions. When collateral circulation is insufficient, and thus cerebral vascular reserve capacity is inadequate, the risk for stroke increases, particularly because microemboli have a higher possibility of becoming symptomatic in the hypoperfused areas (22).

Cerebral perfusion changes, such as an asymmetry in the hemisphere corresponding to the affected carotid artery, have been observed in patients with unilateral severe carotid stenosis, however without a direct correlation to the degree of stenosis (23,24). A measure of perfusion disturbance as provided by cerebral blood flow (CBF) and mean transit time (MTT) appears to be helpful in evaluating brain with a risk of developing a stroke and eventually in guiding the therapeutic decisions especially in acute ischemic events (25).

Positron-emission tomography (PET), single-photon emission CT (SPECT), xenon-enhanced CT (Xe-CT), perfusion CT (PCT), and MR imaging have all been applied in the study of brain hemodynamics. However, the scarce availability of PET and SPECT in most radiology departments has drawn attention for >20 years toward Xe-CT, and it has demonstrated the accurate measurement of perfusion (26, 27). Thus Xe-CT has permitted the differentiation of patients with normal CBF from those with reversible neurologic deficits (CBF = 10–20 mL/100 g per minute) or those with infarction (CBF <10 mL/100 g per minute) (27, 28).

Advances in MR technology have enabled the in vivo acquisition of high-quality multisection echo-planar images of the cerebrum with subsecond temporal resolution. Chelates of gadolinium, a rare earth metal, are commonly used as exogenous contrast agents in MR imaging (28). These chelates have a modulatory effect on both the T1 and T2* of tissue within their sphere of influence. Coupled with a fast T2*- weighted imaging technique, the detection of the passage of a bolus of exogenous contrast agent as it passes through the capillary bed provides a method for spatially mapping the perfusion characteristics of the cerebral parenchyma (11).

Here in this study, we have utilized, both the diffusion weighted and perfusion weighted MR sequences and have reported on our experience on the new lesions appearing in DWI and the changes in the microhaemodynamics detected with perfusion weighted imaging, following stenting of the carotid arterial stenosis.

Aims and Objectives

AIMS AND OBJECTIVES

- To assess the incidence of silent cerebral ischemic insults detectable with DWI after the stenting procedure.

- To evaluate the role of cerebral protection during the stenting procedure as an effective method to reduce the number of silent cerebral ischemic events.

- To measure MR brain perfusion hemodynamic parameters in the cerebral hemisphere supplied by the severely stenotic internal carotid artery (ICA), in a group of patients undergoing an endovascular treatment with a protection device.

- To assess the changes in the MR brain perfusion parameters following carotid stenting.

Review of Literature

REVIEW OF LITERATURE

Carotid artery stenosis involving the origin of the internal carotid artery is a frequent clinical problem. These stenosis, almost invariably atherosclerotic, can present as asymptomatic bruits discovered on physical examination, one or more transient ischemic attacks related to embolization of thrombus from stenotic lesions or to hypoperfusion, or less commonly, as an ischemic stroke.

IMAGING THE CAROTID BIFURCATION

Treatment of extracranial carotid artery disease has been one of the most hotly debated topics in vascular medicine. Imaging of the carotid bifurcation remains an important first step in the therapeutic decision-making process. Successful determination of the severity of carotid artery stenosis depends on several factors, including the skill and expertise of the sonologists. Knowledge of the advantages and pitfalls of the specific technology; and the need for correlative imaging based on initial test findings (29).

Imaging of the carotid bifurcation can be done by carotid Doppler ultrasonography, CT angiogram and MR angiogram. Digital subtraction rotational angiography still remains the gold standard in accurate grading of the stenosis.

DOPPLER ULTRASONOGRAPHY

Initial Doppler criteria proposed by Fel and colleagues utilized frequency measurements of the spectral waveform to predict internal carotid artery stenosis (30). Subsequently, alternate criteria were developed that have resulted in excellent sensitivity and specificity of duplex sonography to determine high-grade stenosis (31) (Table 1).

Meta-analyses of published criteria for carotid duplex ultrasonography have demonstrated sensitivities of 98% and specificities of 88% for detecting >50% internal carotid artery stenosis; and 94% and 90%, respectively, for detecting >70% internal carotid artery stenosis (32) (Fig 1).

Many centers have proposed specific diagnostic criteria, and this variability prompted a multispecialty consensus conference that determined optimal criteria based on a review of the published literature (33) (Table 2).

The carotid duplex examination also identifies plaque, stenosis, and occlusion in the common, internal, and external carotid arteries. It identifies the direction of flow in the vertebral arteries. Doppler examination is routinely performed for patients with a history of transient ischemic attacks or stroke, after surgical or endovascular revascularization, and in patients deemed to be at high risk for presence of carotid stenosis.

With increasing interest in carotid artery stenting as primary treatment for extracranial carotid artery disease, and clinical trials reporting variable rates of carotid stent restenosis at 1 year ranging from 5% (34) to 18.5% (35), accurate methods of stent surveillance are critical. CDUS seems like the ideal method of stent follow-up, given the fact that it is noninvasive, painless, inexpensive, and will not be adversely impacted by the stent components.

Table 1: Doppler Ultrasound Criteria For Internal Carotid Artery Stenosis

Stenosis Severity(%)	**PSV (cm/sec)**	**EDV (cm/sec)**	**Spectral Broadening**
1-14	<125	NA	None
15-49	<125	NA	Present
50-79	>125	<40	Present
80-99	>125	>40	Diffuse
Occluded	0	0	NA

Abbreviation: PSV - Peak Systolic Velocity, EDV - End Diastolic Velocity NA – Not Applicable.

Table 2: Society For Radiologists In Ultrasound Consensus Guidelines

Degree of stenosis (%)	**ICA PSV (cm/sec)**	**Plaque estimate**	**ICA/CCA PSV Ratio**	**ICA EDV (cm/sec)**
Normal	<125	None	<2.0	<40
<50	<125	<50	<2.0	<40
50-69	125-230	≥50	>4.0	>100
≥70 but < near occlusion	>230	≥50	>4.0	>100
Near Occlusion	High /Low/ Undectectable	Visible	Variable	Variable
Total Occlusion	Undetectable	Visible, No detectable lumen	Not applicable	Not applicable

Abbreviations: PSV - Peak Systolic Velocity, EDV - End Diastolic Velocity, CCA- Common Carotid Artery, ICA – Internal Carotid Artery.

Early reports suggested that CDUS was less accurate for determining stent patency, as the stent may alter the Doppler derived velocities (36, 37). Although the exact mechanism for alteration in these velocities is unclear, some investigators have suggested that alterations in compliance of the internal carotid artery after CAS results in elevations in peak systolic velocities. This may thereby require new criteria for the stented internal carotid artery (38). However, recent data demonstrating restenosis rates after CAS utilized Doppler velocity criteria unchanged from native internal carotid arteries (35).

Although large-scale prospective multicenter comparative studies of CDUS with contrast arteriography for evaluation of in-stent restenosis have yet to be published, some investigators have suggested that interval increase in peak systolic velocity $\geq$80% over the baseline postprocedure DUS is the best predictor of in-stent restenosis (39). Many investigators have proposed specific velocity criteria for the diagnosis of patent and stenotic carotid stents during surveillance duplex ultrasonography (Table 3).

Recently, investigators have proposed that specific patterns of in-stent restenosis may actually predict the need for repeat intervention. In one series of 85 in-stent restenosis lesions among 255 patients, those lesions with diffuse proliferative in-stent restenosis that extended beyond the confines of the stent were more likely to require repeat intervention. This pattern ("type IV restenosis"), along with the presence of diabetes mellitus, was the only independent predictor of the need for subsequent reintervention on multivariate analysis (47).

Table 3: Carotid Stent Duplex Ultrasonography Criteria.

Study First Author	No of Patients	Stenosis (%)	PSV cm/s	EDV cm/s	ICA / CCA	Sensitivity (%)	Specificity (%)
Lal[38]	26	≥20	>150	NA	≥2.16	100	98
Peterson[40]	158	>50	>170	>120	NA	100	100
Stanziale[41]	118	≥70	≥350	NA	≥4.75	100	96
Chu[42]	260	≥70	≥450	NA	≥4.3	67	
Aburahma[43]	93	≥30	155	NA	NA	100	90
Zhou[44]	237	>70	>300	>90	>4.0	94	50
Lal[45]	189	≥80	≥340	NA	≥4.15	100	98.6
Setacci[46]	814	≥70	≥300	≥140	≥3.8	99	98

Abbreviations: PSV - Peak Systolic Velocity, EDV - End Diastolic Velocity, CCA- Common Carotid Artery, ICA – Internal Carotid Artery, NA – Not Applicable.

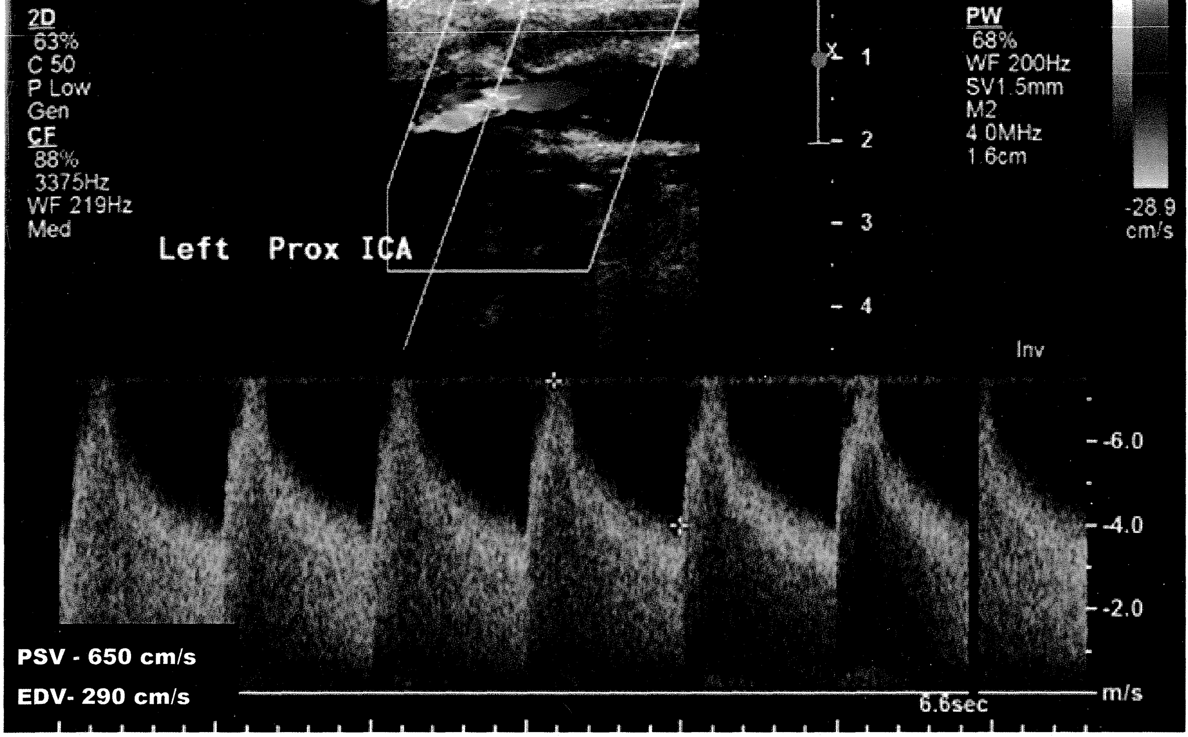


Fig: 1. Color-assisted carotid duplex ultrasonography demonstrating a severe left internal carotid artery stenosis. Note the marked elevation in peak systolic velocity (650 cm/s) and end-diastolic velocity(290 cm/s).

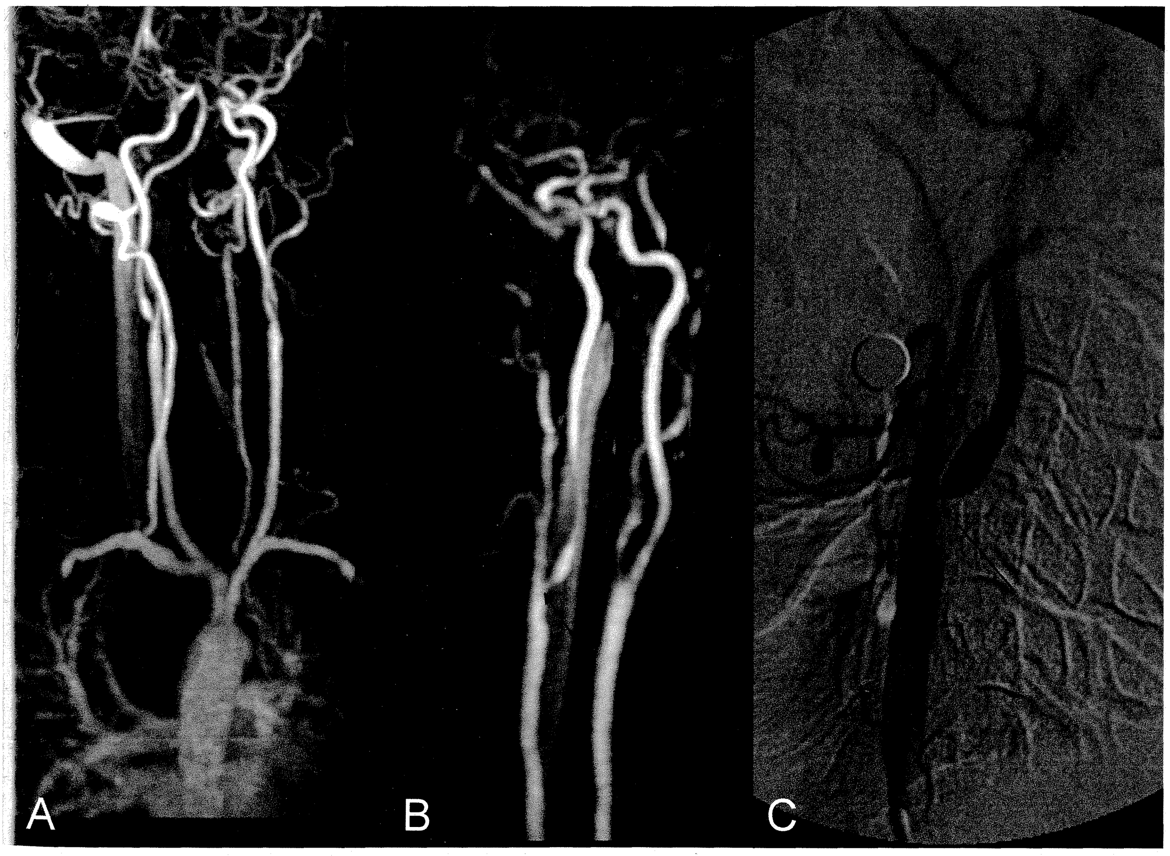


Fig: 2. CEMRA MIP (A and B) images of a patient with right internal carotid artery stenosis in comparison with 2D DSA (C). Note overestimation of the stenosis with CEMRA.

Sensitivity and specificity of MRA for detection of significant ($\geq$70%) carotid stenosis can be difficult to compare between various MRI pulse sequences because of differences in the precise hardware and scanning parameters used in clinical trials.

In several studies that examined MRA as a test for severe stenosis, using DSA as a gold standard, CEMRA demonstrated sensitivity of 87% to 95% and specificity of 46% to 88%; three-dimensional TOF-MRA showed sensitivity of 86% to 94% and specificity of 73% to 100%; and 2D TOF-MRA showed sensitivity of 84% to 94% and specificity of 94% to 97% (50).

Recently, investigators have validated the use of MRA to determine suitability for CAS. In a series of 96 carotid stent procedures, MRA and intraarterial contrast arteriography were performed, and demonstrated that MRA performed quite well in evaluating candidacy for carotid stent (sensitivity and specificity 100%); characterizing aortic arch type (sensitivity 87%, specificity 100%); and identifying carotid artery tortuosity (sensitivity 93%, specificity 100%)(51). In a recent study comparing CDUS to MRA and digital subtraction angiography in 31 patients, CE-MRA was superior to 2D TOF-MRA for confirmation of CDUS findings of carotid occlusion (52).

Due to the composition of carotid stents, MR is a suboptimal examination to determine the patency of carotid stents over time. However, in one series evaluating stents of different metallic compositions, nitinol-based stents performed better than stainless steel or cobalt alloy stents (53). Artificial luminal narrowing (ALN) was evaluated and nitinol stents were found have lower ALN compared to ferromagnetic stents(38% v/s >85%) but still CE-MRA is well suited for the examination of carotid artery stents made of nitinol at both 1.5T and 3Tstrengths.

CT ANGIOGRAPHY

Computerized tomographic arteriography (CTA) has become an important adjunct in the diagnosis of arterial and venous disorders. There are several advantages of CTA over MRA, most importantly the improved spatial resolution resulting in more detailed vascular anatomy. CTA will also provide important information about surrounding soft tissue structures, which may have an impact on therapy (54). Implantable pacemakers and defibrillators are not contraindications to CTA, and claustrophobia appears to be less of an issue with CTA than MRA. Initially, CTA was performed with early-stage equipment with single-row imagers. These scanners took longer to complete image acquisition and were only able to assess relatively small fields of view.

A recent meta-analysis of the diagnostic accuracy of CTA for the assessment of carotid stenosis reviewed 28 studies that compared CTA with DSA (55). CTA was found to be highly accurate for determining degree of carotid stenosis, with overall sensitivity of 97% and specificity of 99%. For 70% to 99% stenosis, CTA was found to be reliable, with sensitivity of 85% and specificity of 93%.

Compared to CDU and MRA, CTA has been found to be appropriate noninvasive method in distinguishing between critical internal carotid artery stenosis and true complete occlusion. The implications of this are potentially important in the selection between surgical and medical treatment (56). One study demonstrated accuracy of 85% in distinguishing between occlusion and the “string sign” with CTA (57) using early stage CT technology.

Multidetector CTA has largely replaced single-row CTA, because this newer technology provides a wider field of view with shorter scan times. In a recent series of 68 patients who underwent multidetector CTA and contrast arteriography or rotational angiography, the sensitivity of multiplanar reformation image analysis was 95% with a specificity of 93% for detecting ≥50% carotid stenosis (58).

CTA is limited in cases where dense circumferential calcification exists (59). In addition, these examinations require administration of iodinated contrast, which carries significant risk among elderly patients, those with diabetes mellitus, and those with preexisting renal disease (60). In addition, there is significant radiation exposure from CTA, potentially resulting in an increased risk of radiation-induced malignancy (61). MDCT radiation dose has increased, ranging from 4.2 msV to 18.1 msV (62). Therefore, CTA is not the ideal first diagnostic test for assessing carotid bifurcation, and is also not an appropriate surveillance examination.

When comparing CDUS with multidetector CT to determine accuracy in carotid artery evaluation, a recent series of 232 patients who underwent both studies suggested that a PSV ≥155 cm/s as measured by CDUS was more reliable in predicting ≥50% carotid artery stenosis than those velocity criteria that are classically reported. However, criteria for determining ≥80% stenosis are comparable to previously reported series, with PSV ≥370 cm/s, end-diastolic velocity ≥140 cm/s and internal carotid artery to common carotid artery ratio ≥6.0 (63).

Some investigators suggest that high-resolution CTA is the ideal surveillance strategy for carotid artery stents (64). In one series of 27 patients who underwent 37 CDUS and CTA examinations to determine the severity of carotid in-stent restenosis, CDUS velocity criteria for >50% in-stent restenosis were PSV>200 cm/s and an internal carotid artery to common carotid artery ratio >2.5. Seven patients also underwent intraarterial digital subtraction arteriography. In this series, Compared with catheter angiography, CTA overestimated percent stenosis from 34% to 66% (mean 53%). US confirmed 2 angiographically proven restenosis, but CTA identified only 1. Finally the authors concluded that CTA was better than CDUS in actually imaging the stent, but determination of in-stent restenosis was more accurate with CDUS (65). Additional large scale multicenter trials will be required to validate CTA in carotid stent stenosis imaging.

DIGITAL SUBTRACTION AND ROTATIONAL ANGIOGRAPHY

Conventional angiography has long been touted as the gold standard for imaging the cerebrovascular system. It is particularly useful in imaging arch type, carotid and vertebral tortuosity, and stenosis as well as intracranial pathology, such as aneurysms or arteriovenous malformations. While single plane angiography may underestimate tortuosity and/or stenosis when imaged in non-orthogonal planes, the use of biplanar or rotational angiography can correct for these mistakes. Since angiography is an invasive procedure, it poses risk of access-site injuries, including bleeding and dissection, as well as contrast-induced anaphylaxis, nephrotoxicity, and atheroemboli. Risks for transient or permanent neurologic deficits following cerebral angiography range from 0.3% to 5.7% (66).

A recent review of 19,826 consecutive patients who underwent cerebral catheter angiography from 1981 to 2003 by Kaufmann et al (67) showed an overall neurologic complication rate of 2.63%, with increased risk in patients with known cerebrovascular disease and/or symptoms such as transient ischemic attacks. Factors independently associated with a decreased risk of neurologic complications included the chronologic year in which the procedure was performed. The latter may be related to improved equipment and procedural technique. Alternatively, the advent of other noninvasive imaging studies, such as MRA and CTA, may have helped screen for high-risk patients with occult cerebrovascular disease or difficult arch anatomy, thus selecting a lower-risk cohort for angiography. Indeed, in most cases, noninvasive imaging has come to replace and, in some instances (ie, assessment of plaque morphology), has surpassed conventional angiography in guiding treatment for carotid artery disease.

Presently role of digital subtraction angiography is two fold. One indication is that if the two noninvasive tests are discordant in grading stenosis (ie, CDUS demonstrates 70% to 99% stenosis, but CTA reveals 50% stenosis). And the other is when the patient is being considered for the carotid artery stenting.

Finally a recent meta-analysis evaluated 41 published studies of carotid artery imaging between 1980 and 2004 using CDUS, MRA, and CTA. Sensitivity and specificity for detecting 70% to 99% internal carotid artery stenosis was 94% and 93% for CE-MRA; 89% and 84% for CDUS; 88% and 84% for MRA; and 76% and 94% for CTA (68). This study suggests that the decision analysis for carotid bifurcation imaging must be based on local expertise.

PLAQUE MORPHOLOGY

Presence of atherosclerosis in the carotid artery places patients at increased risk of transient ischemic attack or stroke. While degree of stenosis is used most commonly to determine suitability for carotid revascularization, plaque morphology has been shown to confer separate risks for developing symptoms as well. Similar to the atherosclerosis elsewhere in the body, the carotid plaque consists of a fibrous cap over a soft central core of lipids and necrotic material. The remainder of the plaque is composed of fibroblasts, smooth muscle cells, and calcification (69). Plaque rupture is thought to be the precipitating event leading to thrombosis or atheroemboli and an ischemic event (70).

Ultrasonography, using echogenicity, is able to characterize plaque morphology and can serve to identify the vulnerable or unstable plaque. Several studies have shown that soft, echolucent plaques appear to be at higher risk of developing symptoms than nonecholucent, hard plaques (71, 72). Morphometric analysis of 78 symptomatic plaques following endarterectomy found that echolucent plaques contained more lipid ($P= .01$) and less calcification and fibrous tissue ($P = .03$) than echo-rich plaques. Intraplaque hemorrhage was directly related to the amount of lipid and inversely related to the fibrous content in the plaque (73). This association between lipid contact and hemorrhage may help explain the increased incidence of symptoms in echolucent plaques. While Doppler ultrasonography has been at the forefront of plaque characterization research, it is highly operator-dependent and qualitative. Moreover, calcified bifurcations are problematic as shadowing may obscure underlying noncalcified plaque preventing adequate assessment.

Evolving technology using CTA and MRA promises even greater ability to characterize plaque composition and morphology. MR imaging has the potential to distinguish all the major plaque components using different contrast weightings (74). Initial experiments involving imaging of endarterectomy specimens (75), as well as subsequent in vivo imaging studies show that lipid-necrotic core and intraplaque hemorrhage can be identified with sensitivity (85%) and specificity (92%) (76). More recent studies have aimed to quantify various plaque components. In particular, thickness of the fibrous cap and degree of underlying lipid-necrosis may particularly helpful in identifying those plaques at greatest risk of rupture.

Using multicontrast MR images, Clarke et al (77) created a "tissue-specific map" of carotid plaque composition and then compared their map to corresponding histology from plaque specimens. Overall accuracy of the MR map compared to histology was 73.5%. In particular, the position and thickness of the fibrous cap separating necrotic core from lumen correlated well with histology. Disruption of the fibrous cap, perhaps the penultimate event prior to rupture has also been studied with MRA. Preoperative images from 22 carotid plaques were compared to specimen histology and found to have a high level of agreement with regard to the integrity of the fibrous cap (intact-thick, intact-thin, or ruptured) ($k = 0.83$) (78).

Intraplaque hemorrhage, commonly found in unstable plaques, is also detectable using magnetic resonance imaging (MRI). Furthermore, it has been shown that hemorrhage of various ages can be differentiated as well (79). The potential clinical significance of detecting intraplaque hemorrhage was addressed by Altaf et al (80, 81).

Preoperative MRI performed on 60 patients with high-grade symptomatic carotid stenosis revealed intraplaque hemorrhage in 36 patients (60%). Transcranial Doppler at the time of surgery showed an association between intraplaque hemorrhage and the presence of microemboli produced during the dissection phase of endarterectomy. The authors conclude that MRI detection of hemorrhagic plaque may predict particulate embolization during surgery and may assist in identifying those patients who may be at higher operative risk. A separate study by the same authors showed that intraplaque hemorrhage detected by MRI can predict recurrent ischemic events in patients with high-grade symptomatic stenosis (80). Of 66 patients studied (median follow-up of 33.5 days), those with intraplaque hemorrhage had a higher likelihood of developing recurrent ischemic events (hazard ratio = 4.8; 95% confidence interval = 1.1 to 20.9, $P < .05$). While there is some debate as to the optimal waiting period for endarterectomy following a stroke, this study would suggest that one should not delay surgery unnecessarily in those symptomatic patients found to have intraplaque hemorrhage on MRI.

Similar to MRI, CTA has tremendous potential for plaque characterization. It is especially suited for analysis of heavily calcified plaques, which are prone to decreased signal intensity and artifact distortion on MRI and shadowing on Doppler ultrasonography. CTA also carries the advantage of being semi-objective, quantitative, and potentially reproducible, whereas MRI lacks standardization among different centers in terms of scanner platform, sequence protocol, and coil design. CTA uses attenuation values (Hounsfield units) to measure density in order to distinguish among plaque features, such as calcium, lipid, and fibrous stroma (82).

Several studies have shown that plaque density may serve as a marker to identify those patients at high-risk for ischemic stroke (83-86). While earlier studies using single-detector scanners showed only mediocre agreement between plaque density and histology,(87) the multidetector scanners have proven to be more accurate, especially with regards to calcium (83,88).

Quantification of calcium from carotid plaques using multidetector CTA in 26 patients with severe stenosis showed good correlation with estimations derived from weight of ashed specimen remnants (k = 0.911, $P < .005$). These authors also found that a lower content of calcium was associated with a greater prevalence of neurologic symptoms (89). Others have shown that the proportion of plaque calcification rather than absolute volume is associated with stability in patients with carotid stenosis.

Nandalur et al (84) used CTA to study 102 patients with >50% stenosis using NASCET criteria and found that >45% calcification of the total plaque was very specific for the absence of symptoms. These results may have theoretical application for management of patients with asymptomatic carotid stenosis. As the margin of benefit in this group of patients is more modest than for those with symptomatic lesions, the role of calcification may be useful in identifying a subgroup (i.e. those with >45% plaque calcification) that might be treated less aggressively.

In addition to providing useful analysis of plaque composition, CTA may also help in the evaluation of the ulcerated plaque in carotid stenosis.

Randoux et al (90) examined 44 carotid arteries with CTA, CEMRA, and DSA and found a significant correlation among the three for degree and length of the stenosis. Detection of severe stenosis was highly accurate with CTA (100% sensitivity; 100% specificity) and CEMRA (93% sensitivity; 100% specificity). Moreover, surface irregularities were more frequently appreciated with CTA than DSA or CEMRA.

A more recent study analyzed stenosis degree, plaque compositions and ulcerations using CTA, duplex ultrasonography, and surgical findings (91). CTAs superiority (sensitivity, 93.75%; specificity, 98.59%) compared with duplex ultrasonography (sensitivity, 37.5%; specificity, 91.5%) may relate to calcium shadowing obscuring ulcerations during duplex ultrasonography. Accurate detection of ulcerations in preoperative images is of great clinical value, as it may change the therapeutic approach (Stent *v* CEA) and likely heightens awareness during carotid bulb manipulation.

Although angiography is superb for assessment of stenosis severity and calcification, it is less reliable for evaluating plaque morphology. In one study, catheter-based angiography had a sensitivity of 46%, specificity of 74%, and positive predictive value of 72% for detecting histologically confirmed plaque ulceration. (92, 93).

TREATMENT OF CAROTID STENOSIS

Multiple trials have attempted to evaluate the role of CEA in those patients with symptomatic carotid stenosis. The two major prospective randomized trials comparing CEA to optimal medical therapy are the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (4, 94) and the European Carotid Surgery Trial (ECST) (95, 96). These two trials helped to clearly define the role of CEA versus optimal medical therapy for patients with symptomatic carotid stenosis.

An important distinction between these two trials was the method used to calculate degree of stenosis. The NASCET study measured the degree of stenosis by taking the luminal diameter at the maximal stenosis and comparing it to the luminal diameter of the portion of the internal carotid artery in which the carotid arterial walls became parallel distal to the area of stenosis. Contrary to this, the ECST study approximated the outer wall diameter at the point of maximum stenosis in the internal carotid artery or carotid bifurcation and then calculated the true luminal diameter at the area of maximal stenosis. The percentage of stenosis was calculated by dividing the minimal luminal diameter by the estimated outer wall diameter. This led to a discrepancy between the two trials, where the NASCET-calculated degree of stenosis was somewhat less than the ECST-calculated degree of stenosis. For example, the same stenosis would be calculated as 80% stenosis by NASCET calculations, but would be almost 90% by ECST methodology. To convert this difference, a formula was calculated by Rothwell et al (97) in 1994 in which the ECST-measured degree of stenosis was equal to 0.6 times the NASCET-measured degree of stenosis plus 40.

The NASCET trial was divided into three major components, all of which required that the patients have symptoms of either a reversible neurologic deficit or a nondisabling stroke within 120 days of randomization. NASCET (severe stenosis) pertained to patients with >70% and <99% stenosis with ipsilateral cerebral symptoms.

NASCET (high moderate stenosis) included those patients with a 50% to 69% stenosis of the ipsilateral carotid artery relative to the cerebral vascular symptoms, and finally NASCET (low moderate stenosis) included those patients with <50% degree of stenosis of the internal carotid artery ipsilateral to the symptomatic hemisphere.

The NASCET (severe stenosis) study involved 50 centers throughout the United States and Canada, and over 1,600 patients were enrolled in the randomized trial. The trial was scheduled to proceed for 5 years, but due to a statistically significant difference in favor of CEA compared to maximal medical antiplatelet therapy with aspirin, the study was stopped by the Safety Committee at 2 years because it was felt to be unethical and unsafe to continue.

The initial results for the NASCET (severe stenosis) group of patients with a 70% to 99% stenosis revealed an ipsilateral stroke risk of 24.5 % in the medical group versus an 8.6% risk of stroke in the surgical group. This resulted in an absolute risk reduction of 15.9%, which was statistically significant. The number needed to treat with CEA to prevent one stroke compared to antiplatelet therapy with aspirin alone was six patients. When these patients were followed for 5 years, the ipsilateral risk of stroke was 28% in the medical group compared to 13% in the surgical group. The crossover of patients randomized medical therapy, but receiving surgical therapy was approximately 6.3%. The number of patients that were originally randomized and treated in the medical arm but then developed symptoms or progression of disease that underwent surgical intervention was approximately 7.9%. Despite undergoing a surgical intervention, if the patient did not sustain one of the primary endpoints of stroke or death they were considered a success of medical therapy.

Those patients that originally randomized as surgical but received only medical therapy were approximately 0.3% for the 70% to 99% stenosis arm of NASCET.

The NASCET (high moderate stenosis) trial was actually carried out for 5 years and focused on patients with 50% to 69% stenosis and ipsilateral symptoms (98). There were 2,226 randomized to either medical therapy (n = 1,118) or CEA (n = 1,108). Of those patients randomized, 858 patients underwent therapy (1,368 had stenosis <50% and were excluded from this portion of the study, but were included in the <50% low moderate stenosis arm of the trial). The 5-year risk of ipsilateral stroke or death for the medical group was 22.2% and for the CEA group 15.7%. (P =.045). This resulted in an absolute risk reduction of 6.5% and a relative risk reduction of 29%. These findings were again consistent with that of the 70% to 99% stenosis group, revealing a significant advantage of CEA over medical therapy with aspirin. A similar result was found in the NASCET (low moderate stenosis) group of the 0% to 49% stenosis, despite the presence of symptoms. In this arm, they found that at 5 years, there is an 18.7% risk of ipsilateral stroke in the medical group and a 14.9% risk of ipsilateral stroke in the surgical group. Certainly, this trend is favorable, but was not statistically significant. The risk of a disabling stroke for the medical group was 4.7% and for the CEA group was 4.6%. The any stroke or death rate was 37% (medical) and 36.2% (CEA) (P = .97).

The ECST was a randomized controlled trial based on intention to treat with a follow-up of more than 6 years. More than 3,000 patients were randomized in Europe and Australia in 97 centers.

Patients were required to have an ischemic cerebral vascular event (TIA, amaurosis fugax, or nondisabling stroke) in a distribution ipsilateral to a carotid stenosis >60% within 6 months of randomization. Differing from the NASCET, the ECST also allowed for what was termed the physician uncertainty principal. Patients that the physician felt were best treated with surgical endarterectomy were placed in the endarterectomy arm, whereas those patients that the physician felt the patient would be best served with medical therapy with aspirin were placed in the medical treatment arm. Only those patients that the physician was "uncertain" were randomized between the two arms of the trial. Patients randomized to CEA were encouraged to have surgery as soon as possible. There was a 3.5% medical to surgical therapy crossover and a late crossover to CEA of 8.3% at 1 year after randomization, secondary to patient wishes or recurrent symptoms. The surgical to medical crossover arm was 3.4%. The outcome for the 70% to 99% stenosis group with the 3-year stroke or death risk of the medical group was 22% versus 12% in the surgical arm. This resulted in an absolute risk reduction of 10% in favor of CEA versus medical therapy. The 30-day surgical ipsilateral stroke or death rate was 7.5% for the 70% to 99% stenosis by the European carotid stenosis calculations, and for those lesions <70% already in the mild-to-moderate stenosis, there is no advantage to CEA and, in fact, it actually was found to be harmful compared to best medical therapy. Cina and colleagues (99) prepared a combined analysis of the NASCET and ECST trials and grouped the data based on calculated degree of stenosis. With an endpoint of any disabling stroke or death, they report a statistically significant advantage for symptomatic patients with an ipsilateral stenosis >50%.

For patients with a NASCET equivalent to 70% to 99% symptomatic stenosis (n = 1,247) the odds ratio (OR) was 0.48 (95% confidence interval [CI], 0.33-0.70) in favor of CEA. For the NASCET equivalent 50% to 69% stenosis, OR was 0.69 (95% CI, 0.51-.94). For a symptomatic stenosis of <50% the OR was 1.23 (95% CI, 1.00-1.51) (99).

The third prospective randomized trial was the Veterans Affairs Cooperative Studies Program 309 trial, but this trial was discontinued approximately midway through its course because of the publication of the results of both the NASCET and the ECST trials.

From the results of these three high-quality prospective randomized trials (4,100,101), it has become apparent that symptomatic stenoses that narrows the diameter of the carotid artery more than 60% to 70% lead to a significant incidence of stroke if treated medically (102).

Based on clinical data showing lack of inferiority of CAS to CEA (16,101,103) use of CAS has been extrapolated to be an alternative to CEA in medical or surgical high-risk patients deemed appropriate to undergo carotid intervention.

There are multiple studies randomizing endovascular treatment of carotid stenosis with carotid stenting angioplasty with surgery or with medical therapy in those patients with symptoms. These studies include the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)-Medical (104,105), CAVATAS-CEA (6), the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) (106-108), Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) (103), and Stent Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) (107,109,110) trials.

CAVATAS enrolled 550 patients with 505 patients having a carotid artery stenosis suitable for surgical intervention. There were also 40 patients who were felt not suitable for CEA and underwent maximal medical therapy and were enrolled in CAVATAS-MED. The major concern with the CAVATAS study was that the majority of the patients were treated with angioplasty alone and only 26% were actually treated with angioplasty and stenting. The 30-day stroke or death rate with CAVATAS per CAS was 10%, whereas for CEA it was 9.9%.

The EVA-3S trial was a French multicenter randomized trial with national funding (106-108). Symptomatic patients were with an associated artherosclerotic plaque within the ipsilateral carotid of at least 60% by NASCET criterion were included in the study. The patient had to be deemed eligible for either CEA or CAS. The trial was stopped secondary to the concern for ethical and safety reasons of continuing the trial, because there was a significant difference between the CEA group and the CAS group. The inexperience of the interventionalist performing the CAS procedures has led to criticism of the trial design and potentially leading to the high rate of complications in the CAS group. Overall 30-day any stroke or death rate for CEA was noted to be 3.9% versus 9.6% in the CAS group. The 30-day incidence of disabling stroke or death for CEA was lower than CAS (1.5% *v* 3.4%). The 6-month any stroke or death rate was again lower in the CEA group compared to CAS (6.1% *v*11.7%). Not unexpectedly, the cranial nerve injury rate was significantly higher in the CEA at 7.7% compared to a 1.1% instance in the carotid angioplasty and stenting group.

The significant differences between the CAS and the CEA groups resulted in the stopping of the EVA-3S trial, stating it was unethical and unsafe to continue the trial with such a dramatic difference in favor of CEA.

The Carotid Revascularization Using Endarterectomy or Stenting Systems (CARESS) trial was a direct comparison of CEA versus CAS stent using embolic protection (111,112). It was a multicenter prospective nonrandomized trial with a 2:1 randomization of CEA to CAS. Within this trial, 32% were symptomatic and 68% were asymptomatic. The findings of this trial revealed that there is no significant difference in combined stroke or death rate at 30 days between CEA (3.6%) and CAS (2.1%) or at 1 year, CEA (13.6%) versus CAS (10%). This study was believed to show equivalency of CAS with CEA with endpoints of stroke, death, or myocardial infarction.

The SPACE trial was a multicenter randomized trial for patients with symptomatic carotid stenosis >70% by duplex (107,109,110). A total of 1,183 patients who had symptoms from a carotid stenosis within 180 days were randomized to either CAS or CEA. Patients had to be treated within 14 days of randomization. The primary outcome event was ipsilateral stroke or death within 30 days of intervention. Based on intention-to-treat analysis, there were 42 primary events within the CAS group (6.9%) and 38 events in the CEA group (6.5%). Results of this trial showed no statistically significant inferiority of CAS to CEA. This differed considerably from the opinion of the original EVA-3S trial.

Ringleb et al (113) performed a meta-analysis looking at the outcomes of CAS to CEA. The trials included in the meta-analysis were the Leicester, Wallstent trial, CAVATAS, the Kentucky-A trial, the Kentucky-B trial, the SAPPHIRE trial, EVA-3S trial, and SPACE trial. This is a combination of both symptomatic and asymptomatic patients with 89% symptomatic patients. Within this meta-analysis, there was a 37% increase in the odds of suffering a disabling stroke or death with using CAS compared CEA (OR = 1.37; 85% CI [Confidence interval], 0.92-2.04; *P* =.12). In the analysis of symptomatic patients, the OR was 1.13 with a CI of 0.89 to 1.93 (*P* = .17). The main result is that surgical treatment still remains the gold standard for treatment of patients with symptomatic carotid artery stenosis, who do not have an increased surgical risk. Carotid artery stenting is neither safer than nor as safe as carotid endarterectomy in large clinical trials when short-term stroke and death rates are taken into account.

HAEMODYNAMIC ALTERATIONS SECONDARY TO STENOSIS

Although hemodynamically significant stenoses (meaning, capable of causing local hemodynamic change at the point of stenosis and considered over 70% based on NASCET criteria) are frequently encountered in clinical practice, hemodynamic stroke conversely is rather rare. Nevertheless, the risk of developing an ischemic event is higher in patients with reduced cerebrovascular reactivity than in those in whom cerebrovascular reactivity is preserved (22). For this reason, different tools have been proposed to test cerebral hemodynamics.

Transcranial Doppler sonography represents a noninvasive and reliable technique that has been used in the last few years to measure, in the intracranial arteries, the flow variations in response to dilatatory stimuli (Acetazolamide, CO2 inhalation, apnea) (114). Other imaging techniques to study cerebral hemodynamics are PET, SPECT, CT perfusion and MR perfusion-weighted imaging.

Perfusion- weighted MR imaging allows the evaluation of some fundamental parameters to study cerebral hemodynamics, such as rCBV, relative cerebral blood flow, and rMTT. It can be easily performed as completion of a standard brain MR examination, with a small increase in the time and costs of the imaging technique. (115).

Kluytmans et al (116) evaluated the possible hemodynamic changes caused by a severe ICA stenosis and the subsequent changes after CEA using dynamic susceptibility contrast MRI. He compared the various haemodynamic parameters in 19 patients with severe stenosis (>70%) of the ICA before and after CEA and also in 33 control subjects. He concluded that in the hemisphere ipsilateral to the stenosed ICA, no significant differences were found for the rCBV or MTT between patients and control subjects. Also, no significant alterations in these two parameters were observed after CEA. In the hemisphere contralateral to the stenosed ICA, hemodynamic changes were observed only in patients with an ICA occlusion contralateral to the stenosed ICA. In these patients, rCBV, MTT, time of appearance, and time to peak were all increased in the contralateral hemisphere. After CEA, all hemodynamic parameters fell in the normal range.

Maeda et al (117) assessed the hemodynamic status in symptomatic patients with severe carotid occlusive disease using echo-planar perfusion imaging and showed statistically significant difference in the rMTT values between the affected and the unaffected brain tissue. No significant difference was seen in rCBV values.

In a correlative Assessment of Hemodynamic Parameters Obtained with T2*-weighted Perfusion MR Imaging and SPECT in Symptomatic Carotid Artery Occlusion, Kim et al (118) found that there was normal-to-increased CBV, prolonged uncorrected MTT, decreased CBF, and normal-to-diminished vascular reserve capacity in the affected vascular territories.

Bozzao at al (115) compared the Hemodynamic Modifications in Patients with symptomatic unilateral stenosis of the internal carotid artery with normal control subjects using perfusion-weighted MR imaging and DSA they did not find any significant difference in rCBV and MTT values between the hemispheres in the symptomatic patients. Significant difference in MTT values in the border zones between patients and control subjects was documented.

Incidence of hyperperfusion syndrome following carotid revascularization is relatively low (0.4- 1.8%) (119,120-124).Though the incidence is very rare, the prognosis of the patients with this condition is relatively poor. In addition, a recent study has demonstrated that postoperative cerebral hyperperfusion, even when asymptomatic, is associated with impairment of cognitive function in patients who have undergone CEA (125).

Risk factors for cerebral hyperperfusion include longstanding hypertension, high-grade stenosis, poor collateral blood flow, and contralateral carotid occlusion, which often result in impairments in cerebral hemodynamic reserve (126). Furthermore, a rapid restoration of normal perfusion pressure following CEA may result in hyperperfusion in regions of the brain in which autoregulation is impaired due to chronic ischemia. This hypothesis is similar to the "normal perfusion pressure breakthrough" theory described by Spetzler et al (127) and is consistent with observations by several investigators that decreased cerebrovascular reactivity to acetazolamide is a significant predictor of post-CEA hyperperfusion (128-130).

In hyperperfusion syndrome, Post revascularization SPECT demonstrates an increase in CBF of >100% compared with preoperative values (128-130). Furthermore, patients without postoperative CBF increase of >100% compared with preoperative values usually do not experience hyperperfusion syndrome (128-130). Fukuda et al correlated preoperative cerebral blood volume (CBV) measured by perfusion weighted MR imaging (PWI) with hyperperfusion syndrome and found that no patients with normal preoperative CBV exhibited post-CEA hyperperfusion. He concluded that elevated preoperative CBV was the only significant independent predictor of post-CEA hyperperfusion (131).

NEW BRAIN LESIONS AFTER CAROTID REVASCULARIZATION

Although carotid angioplasty / stenting has been found to be a reasonable alternative to endarterectomy, with acceptable complication rates (17,132,133), a high incidence of emboli shed to the brain has generated great concern regarding the safety of the technique. In fact, higher embolization rates during CAS compared to surgery have been reported using either transcranial Doppler sonography to monitor microembolic events or applying diffusion-weighted imaging (DWI) to detect new embolic brain lesions after the intervention (134-136).

In a systematic review of literature and a total of 2117 patients, Schnaudigel et al has demonstrated that the incidence of any new DWI lesions is significantly higher after endovascular than after surgical treatment of a carotid stenosis (137). Moreover, the data also indicated that the use of a cerebral protection device and a closed-cell stent in CAS as well as selective shunting during CEA significantly reduce the occurrence of new ipsilateral DWI lesions after carotid interventions.

Patients submitted to CAS had a significantly higher incidence of new DWI lesions (on average 37%) than patients treated with CEA (on average 10%). This significantly higher incidence points to an increased risk of periprocedural embolism during CAS as opposed to CEA. Although it is beyond doubt that this finding is largely related to the manipulation of catheters, guidewires, and sheaths in the supra-aortic vasculature, it may also be the consequence of a diagnostic angiography, which is usually performed before CAS. Bendzus et al (20) for instance, detected new DWI lesions in 23 of 100 patients undergoing consecutive diagnostic cerebral angiographies.

When comparing CAS with CEA, it has to be stressed that major technological advances in the field of CAS have occurred in the past few years. Most importantly, there has been a widespread introduction of cerebral protection devices aimed at reducing the passage of embolic material into the cerebral vasculature. Although no randomized study has been conducted as yet to investigate the clinical efficacy of distal protection devices, several case series and stent registries (16,132) clearly support this concept.

In line with this finding, the use of cerebral protection devices appears to significantly reduce the number of new ipsilateral DWI lesions after CAS. However, ≥33% of patients had new DWI lesions within the vascular territory of the treated carotid artery even after protected CAS, which documents that dislodgement of a large number of embolic particles to the brain is not prevented by the use of filter-type protection devices.(137).

Schnaudigel et al (137) also indicated closed-cell stents is associated with a significantly lower incidence of new ipsilateral DWI lesions than the use of open-cell designed stents. This finding could be related to the greater potential of closed-cell stents at preventing continuous embolization attributable to further small particles breaking off the fractured plaque into the blood system and subsequently into the brain. In support of this notion, the use of stents with a closed-cell design was associated with lower periprocedural complication rates in a recent analysis of a dual-center CAS database of 701 consecutive CAS patients (138).

Regarding the potential of an ongoing embolization even after the procedure from a damaged plaque as a result of the manipulation, another retrospective analysis of 3179 consecutive CAS patients could demonstrate a significantly greater rate of postprocedural neurological complications in patients treated with open-cell stents.(139) Only 1 of the studies undergoing review included serial MRI measurements postprocedurally, and the authors found an increase in new DWI lesions depending on the time of scanning (140). Because of the different types of stents used in their study, no statement as to whether there is an association with the type of stent used could be made.

To date, the impact of new DWI lesions after carotid interventions beyond that on manifest neurological complications remains elusive. Especially with regard to subtle neuropsychological alterations, the findings of a significantly greater amount of new DWI lesions after CAS is opposed to a comparable effect of carotid surgery or angioplasty on neuropsychological functions as reported in a sub study of CAVATAS (134).

An evaluation of a possible relationship between cognitive changes and new DWI lesions has been performed in 1 of the studies undergoing review (141). In a group of 10 patients, 4 showed new DWI lesions after CAS. It remains unclear whether cognitive performance had changed in those 4 patients, but the authors report an overall improvement across the whole group in some of the cognitive domains tested.

For a differentiation between the possible benefit of a restored cerebral perfusion that might result in an amelioration of cognitive performance as opposed to the potential harms of microembolic lesions that could lead to cognitive impairment, DWI might contribute to a further elucidation of the effects of carotid interventions on cognitive functions. (137).

Use of covered stents / stent grafts has been advocated for extracranial carotid reconstruction especially when there are associated pseudoaneurysms (142). Usually intimal hyperplasia does not recur in the portion of carotid artery treated with the covered stents (143). More long term follow up is required to determine the potential role of covered stents in cases of recurrent intimal hyperplasia.

Materials and Methods

MATERIALS AND METHODS

The study group consisted of 7 patients (6 male and one female) with mean age of 59 yrs, (range 51 – 66 yrs) who had symptoms consistent with cerebral ischemia or infarction. All the patients were initially screened with Doppler sonography and then MR angiography or conventional angiography if Doppler sonography showed an ICA stenosis of greater than 50% stenosis. Doppler grading of the stenosis was done based on ultrasound consensus guidelines by society for radiologists (Table 2). MRA or conventional Angiography was performed to confirm the presence of severe carotid bifurcation stenosis and to look for significant atherosclerotic disease of the intracranial arterial system. Stenosis on angiography was graded based on NASCET criteria (Fig. 3). Patients with severe stenosis in the ICA (according to the North American Symptomatic Carotid Endarterectomy Trial criteria) (4) and without significant disease other than that at the level of the carotid bifurcation (i.e. an absence of significant tandem lesions) were recruited into this study.

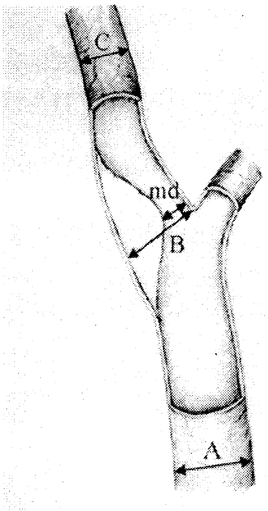


Fig:3. ECST, NASCET and CC Methods for Angiographic Assessment of Carotid Stenosis.
NASCET (1 – md / C) x 100%, ECST (1 – md / B) x 100%, CC (1 – md / A) x 100%

MRI EXAMINATION

MR examinations were performed on a 1.5-T system (Magnetom Avanto Tim, Siemens, Erlangen, Germany) within 1 week to 24 hours before and less than 24 hours after carotid stent placement. The MR protocol included the acquisition of axial images of the brain by using a dual-echo fast spin-echo technique (TR/TE, 2000/20 and 90) and FLAIR technique (TR/TE/TI, 6000/95.9/1800).

DWIs were acquired using single-shot echo-planar imaging (EPI) sequence at multiple levels. 20 slices of 5 mm thickness were obtained (repetition time (TR) 3500 ms, echo time (TE) 105 ms, field of view 40x20, matrix size 230x230, b values of 0 and 1000 $mm^2\ s^{-1}$) in 3 orthogonal directions. ADC maps were made available.

PWI was done by using a multi–time point, single-shot T2*-weighted echo-planar sequence (TR/TE eff, 1800/43; acquisition matrix, 128 x 128 zero-filled before Fourier transformation to 256 x 256; FOV, 25 cm). Sixteen, 5-mm-thick axial sections with interslice gap of 6.5mm were acquired over the cerebrum yielding 50 time points. Exogenous perfusion contrast was provided by a 20-mL bolus of gadolinium diethylenetriamine pentaacetic acid (Omniscan) or Gadolinium- Tetra azacyclodo decane tetraacetic acid (Gd-DOTA/ Dotarem). The bolus was followed by a 20-mL sodium chloride flush administered intravenously by using a power injector at a rate of 5 mL/s starting on the 10th imaging time-point. Parameters used for image acquisition was identical in both pre and post-procedure MR imaging.

Raw PWIs were transferred to a PC workstation (Leonardo, Siemens Medical Systems) for post-processing. With the aid of the implemented software rCBV, rCBF, and rMTT could be calculated on the basis of the indicator dilution method and were displayed as spectral colour images.

Four hemodynamic anatomic ROIs were defined in each cerebral hemisphere as follows: Middle cerebral artery (MCA1) territory and anterior cerebral artery (ACA1) at the level of the basal ganglia.

Similarly ROIs corresponding to MCA2 and ACA2 at the supraventricular level were drawn in each hemisphere (Fig. 4). These ROIs were drawn according to diagrams based on CT studies from Savoiardo (144). From each ROI above mentioned parameters (ratios) both from the ipsilateral and contralateral sides of stenting, before and after stenting procedures were calculated and compared.

STENTING PROCEDURE AND PROTOCOLS

All stent placement procedures in our institute were performed under local anesthesia with stand-by anaesthesiologist in a dedicated single plane angiography suite (Advantx LCV, GE Medical Systems, USA).

PREPARATION FOR THE PROCEDURE

Patients were nil orally from the midnight, the day before the procedure.

Sedation was given on call (May be Pethidine and Phenergan or Morphine, Phenergan).

Catheterization of the patient was done and was shifted on call.

ANTIPLATELET MEDICATION:

It should be started atleast 5 days before the procedure in elective cases. It is 150 – 325 mg / d orally of Aspirin and T. Clopidogrel 75 mg / d (5 days before the procedure). It should be given even on the day of procedure. If it was not started, then T. Aspirin 325 mg and T. Clopidogrel 300 – 450 mg Stat to be given atleast 6 hours before the procedure.

In emergent conditions Inj Abciximab can be started. IV bolus of 0.20 mg / Kg (before intervention and maintenance IV drip of 0.125 mcg / Kg / min (maximum of 10mcg / min) continued for atleast 12 hrs including procedure time. This is given only if stenting is to be done. All the patients in our series, were already on 75 mg of T.Clopidogrel and 150mg of aspirin, so additional extra dose of T.Aspirin / T.Clopidogrel was not given.

If the lesion is secondary to vasculitis and ESR is more than 30mm/ hr, then steroids are to be given. Procedure should be postponed till the ESR comes down to less than 30. In our study, none of the stenosis was secondary to vasculitis.

STENTING PROCEDURE

Materials used in our study for carotid stenting is shown in Table. 4. Vascular access was made under local anesthesia by right common femoral approach in all cases by using an 8F arterial introducer sheath (Cordis). After administration of 5000 IU of heparin, selective catheterization of the CCA was made, and 4 vessel DSA was always performed to confirm the degree of carotid artery stenosis, to evaluate the carotid anatomy and also to decide whether CAS was technically feasible.

Heparin was given hourly 1000 units following initial bolus of 5000 units. Degree of carotid stenosis was calculated according to NASCET criteria. Cross circulation was also studied both across anterior and posterior (ipsilateral to stenosis) communicating arteries. Following angiogram, a stiff guidewire (Terumo, Cordis, USA), was exchanged for a 7F guiding-catheter (Vista Brite, Cordis, USA or Launcher, Medtronic, USA) and it was placed in the ipsilateral CCA. Through guiding catheter, lesion was crossed using 0.014" transcend microguidewire.

Table 4. Materials Used For Angiogram And Stenting

1.	Sheath – Radiofocus, Cordis, Impulse	7, 8 French size
2.	Diagnostic catheters – Vertebral glide (Terumo), Right coronary (Cordis), Mani cerebral (Cordis), Simmons (Cordis)	5, 4 French size
3.	Guide wire – Terumo exchange length, Terumo standard,	150 cm – Standard 260 cms - Exchange
4.	Guiding catheters – Vista Brite, Cordis, USA or Launcher, Medtronic, USA	7, 8 French size
5.	Microguidewires – Transcend	0.014"
6.	Microcatheters – Excelsior 1018 /1010. Echelon 1010	1.4 – 1.8 Fr.
7.	Coronary balloons – Mercury, Abbott. Elect, Biotronics	Usually 3.0mm x 15mm
8.	Protection Devices -- Filter EZ, Boston Scientific, USA or SpideRx, ev3,USA	
9.	Stents -- Protégé, Conical Stent, ev3, USA; Precise or SMART, Cordis, USA	Usually 6mm x 40mm

Neuroprotection device was passed over the micro guidewire and was placed in opened position in the ICA, distal to the stenosis. In six cases, neuroprotection filter device was used. Various types of distal protection devices are currently, commercially available (Table 5). We have used (Fig 5) Filter EZ, Boston Scientific Corporation, USA or SpideRx, ev3, USA in different patients. In one patient stent was deployed without the use of filter, as it was not available at the time of procedure and the risks of embolization was explained before taking for the procedure. In one case predilation with a 3-mm diameter coronary balloon was done before deployment of the filter, as the stenosis was near total and was just allowing the faint opacification of post stenotic vessel (>99%).

After positioning the filter, dedicated nitinol stent of open cell design was passed over the 0.014" guide wire and was deployed across the stenotic site. Various dedicated carotid stents are commercially available (Table 6). We have used Protégé, Conical Stent, ev3, USA; Precise or SMART, Cordis, USA in different patients. In one patient two stents were used as satisfactory position was not obtained with the use of single stent. In 2 cases postdilation with a 5–6-mm diameter balloon was performed. Both dilation procedures were done after injection of 0.125 mg of atropine. A complete check angiogram was performed after all embolization procedures. Heparin was not reversed at the end of the procedure.

Table.5. Currently Approved Carotid Protection Systems and Their Functions.

Device name	Manufacturer	
Percusurge	Medtronic	Distal occlusion balloon
Angioguard	Cordis	Distal filter
Accunet	Abbott (formerly Guidant)	Distal filter
Filterwire EZ	Boston Scientific	Distal filter
Spider	Ev3	Distal filter
Emboshield	Abbott	Distal filter

Table.6. Currently Approved Carotid Stent Systems

Stent name	Manufacturer	Cell type	Tapers	Delivery system size (Fr)
Precise	Cordis	Open	No	6
Acculink	Abbott	Open	Yes	6
Nexstent	Boston scientific	Closed	Self-tapering	5
Protégé	Ev3	Open and Closed	Yes	6
Exact	Abbott	Closed	Yes	6
Exponent	Medtronic	Open	No	6 and 7

POST PROCEDURAL MANAGEMENT

The patient was shifted to the neurological ICU for 48 hours after the procedure and as required. Patient was continued anti-coagulants. Strict monitoring of the blood pressure was done for next 48 hrs (Systolic BP not more than 140 mm of Hg). It was done using oral / parenteral anti-hypertensives. Patient was also observed for the development of additional neurological deficits

STATISTICAL ANALYSIS

In Leonardo work station, spectral colour images of the CBV, CBF and MTT were obtained using indicator dilution method. ROIs defining territories (ACAT and MCAT) of interest were drawn correspondingly in both the hemispheres (Fig 4) in each of the colour maps. Ratios of signal intensities (contralateral normal hemisphere / symptomatic ipsilateral stenotic side hemisphere) were calculated in each of the colour maps to obtain rMTT, rCBV and rCBF. Each of these parametric values obtained before and after the stenting procedure were tabulated and compared. Direct comparison of these parameters between the subjects was not undertaken as Dynamic susceptibility contrast MR technique that was employed was not quantitative. For the statistical analysis, the non-parametric unpaired "T" test was performed. P values < 0.05 were considered statistically significant. Similarly in DWI images obtained before and after revascularization was looked for any new hyperintense lesions and if found were documented.

Results

On the other hand, MTT was more on the stenotic side compared to the contralateral normal hemisphere. No significant asymmetry in the interhemispheric CBV values could be seen CBV colour maps. DWI showed restricted diffusion foci in the involving the right MCA territory in one patient before the procedure. Rest of the patients did not show any acute restricted diffusion ischemic lesions on DWI in the preprocedure stage.

AFTER INTERVENTION

As was the case before intervention, no statistically significant interhemispheric differences in CBV were detected. Compared to preprocedural rCBV value, no statistically significant difference was documented (Fig 7) (Table 8). Following carotid revascularization, increase in the CBF and decrease in the MTT values were noted in all the territories on the stenotic side. Comparing with the pre-procedural values, differences in these parameters were statistically significant with the P value of < 0.05 (Figs 6, 10, 11) (Tables 9 and 10). One patient developed symptomatic infarct involving the anterior temporal lobe of ipsilateral left cerebral hemisphere following protected carotid stenting. It was seen as a hyperintense lesion on DWI and FLAIR (Fig 9). Tiny asymptomatic silent hyperintense DWI lesions were seen in both the hemispheres, ipsilateral (consistent) and contralateral (inconsistent) to stenting in three of the seven patients (Fig 8). Consistent lesions could be seen in all the three patients and It included the above mentioned infarct patient also. On the contrary, two of these three patients showed Inconsistent DWI lesions. One of these three patients, unprotected carotid stenting was done (Table 7).

Table: 7. Demographics, clinical data, new DWI lesions and outcome of the patients.

	Age/ Sex	Type of stenosis*	Symptoms	% Stenosis	Protected CAS	New DWI lesions			Outcome
						Ipsilateral	Contralateral	FLAIR	
1	65Y/M	New	TIA	80	No	Yes	Yes	Nil	No deficits
2	55Y/M	New	Stroke	85	Yes	Nil	Nil	Nil	** Pre Procedural status
3	60Y/M	New	TIA with 3V coronary disease.	70	Yes	Nil	Nil	Nil	No deficits
4	51Y/M	New	TIA.	70	Yes	Nil	Nil	Yes	***Developed deficits
5	66Y/F	New	Chronic Stroke with TIA	75	Yes	Yes	Yes	Nil	No deficits
6	56Y/M	New	TIA	90	Yes	Yes	Nil	Nil	No deficits
7	63Y/M	New	TIA	85	Yes	Nil	Nil	nil	No deficits

*Post RT/ post_CEA / post stent patients.

** : patient had left hemiplegia prior to procedure and the neurological status remained the same after the procedure.

*** : patient developed left temporal lobe infarct and developed right upper limb monoparesis, was delirious and improved subsequently over 5 days.

Table 8: CBV Ratio values obtained by contralateral normal hemisphere / ipsilateral stenotic side in different territories.

	Age / Sex	ACAT 1		MCAT 1		ACAT 2		MCAT 2	
		Pre Pro	Post Pro	Pre Pro	Post Pro	Pre Pro	Post Pro	Pre Pro	Post Pro
1	65Y/ M	0.902	1.035	0.979	1	0.957	0.985	0.98	1.03
2	60Y/ M	0.94	0.985	0.989	1.03	1.02	1.026	1.02	1.01
3	51Y/ M	0.981	1.01	0.999	1.06	1.001	0.983	1.02	0.99
4	55Y/ M	1.062	1.073	1.019	1.14	1.066	1.137	1.008	1.085
5	66Y/ F	0.968	0.957	1.03	0.97	0.957	0.991	0.999	1.009
6	56Y/ M	0.94	1.028	0.988	0.98	0.904	0.996	0.97	0.98
7	59Y/ M	0.991	1.003	0.971	1.02	1.026	0.99	1.019	0.99
Mean		0.969	1.013	0.996	1.028	0.990	1.015	1.002	1.013
S.D		0.050	0.037	0.021	0.057	0.054	0.055	0.020	0.035
P value		0.0858		0.188		0.407		0.48	

CBV : Cerebral Blood Volume, ACAT : Anterior Cerebral Artery Territory, MCAT: Middle Cerebral Artery Territory, Pro : Procedure.

Table: 9 . CBF Ratio values obtained by contralateral normal hemisphere / ipsilateral stenotic side in different territories.

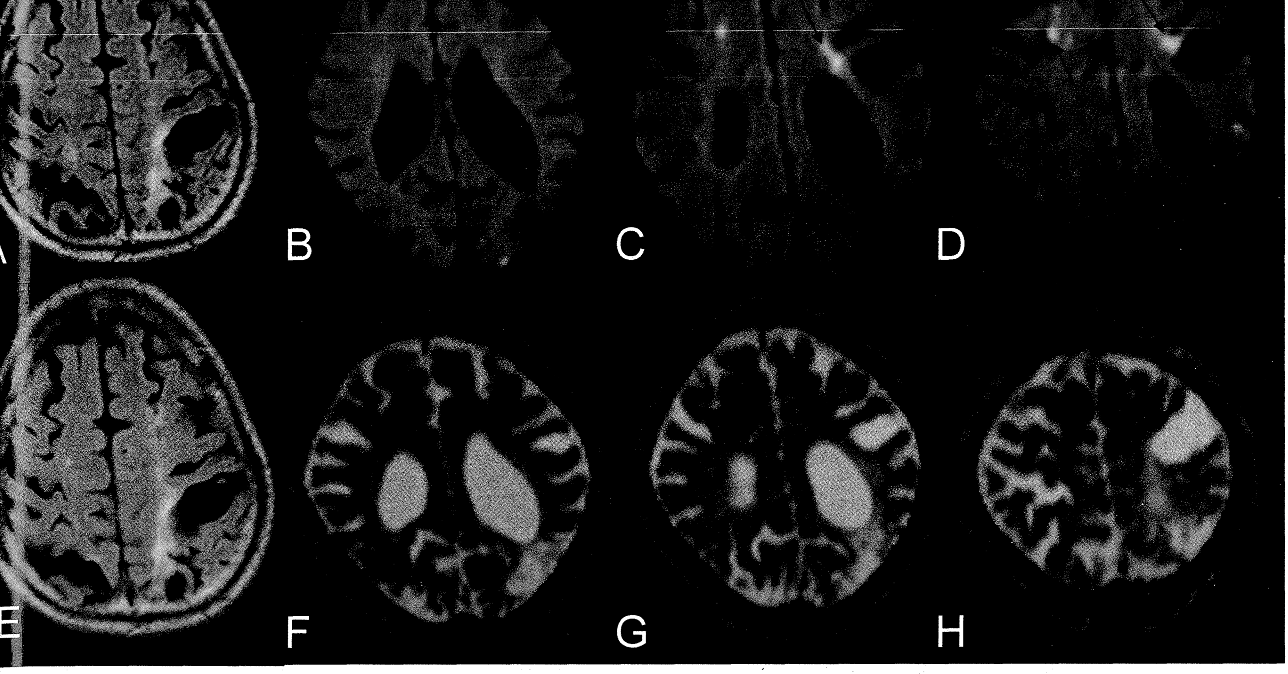
	Age / Sex	ACAT 1		MCAT 1		ACAT 2		MCAT 2	
		Pre Pro	Post Pro	Pre Pro	Post Pro	Pre Pro	Post Pro	Pre Pro	Post Pro
1	65Y/ M	1.1	1.02	1.14	1	1.15	1	1.12	1.01
2	60Y/ M	1.12	1.01	1.16	1.02	1.12	1.02	1.14	1
3	51Y/ M	1.09	0.98	1.1	1	1.11	1.03	1.13	0.99
4	55Y/ M	1.28	1.12	1.24	1.12	1.22	1.14	1.25	1.18
5	66Y/ F	1.1	1.01	1.14	1.03	1.1	0.99	1.14	1.02
6	56Y/ M	1.12	0.99	1.13	0.98	1.13	0.99	1.12	1
7	59Y/ M	1.14	1.01	1.14	0.99	1.14	1	1.1	0.99
Mean		1.136	1.02	1.15	1.02	1.138	1.024	1.143	1.027
S.D		0.066	0.046	0.043	0.047	0.04	0.053	0.049	0.068
P value		0.0026		0.0002		0.0001		0.0034	

CBF : Cerebral Blood Flow, ACAT : Anterior Cerebral Artery Territory, MCAT: Middle Cerebral Artery Territory, Pro : Procedure.

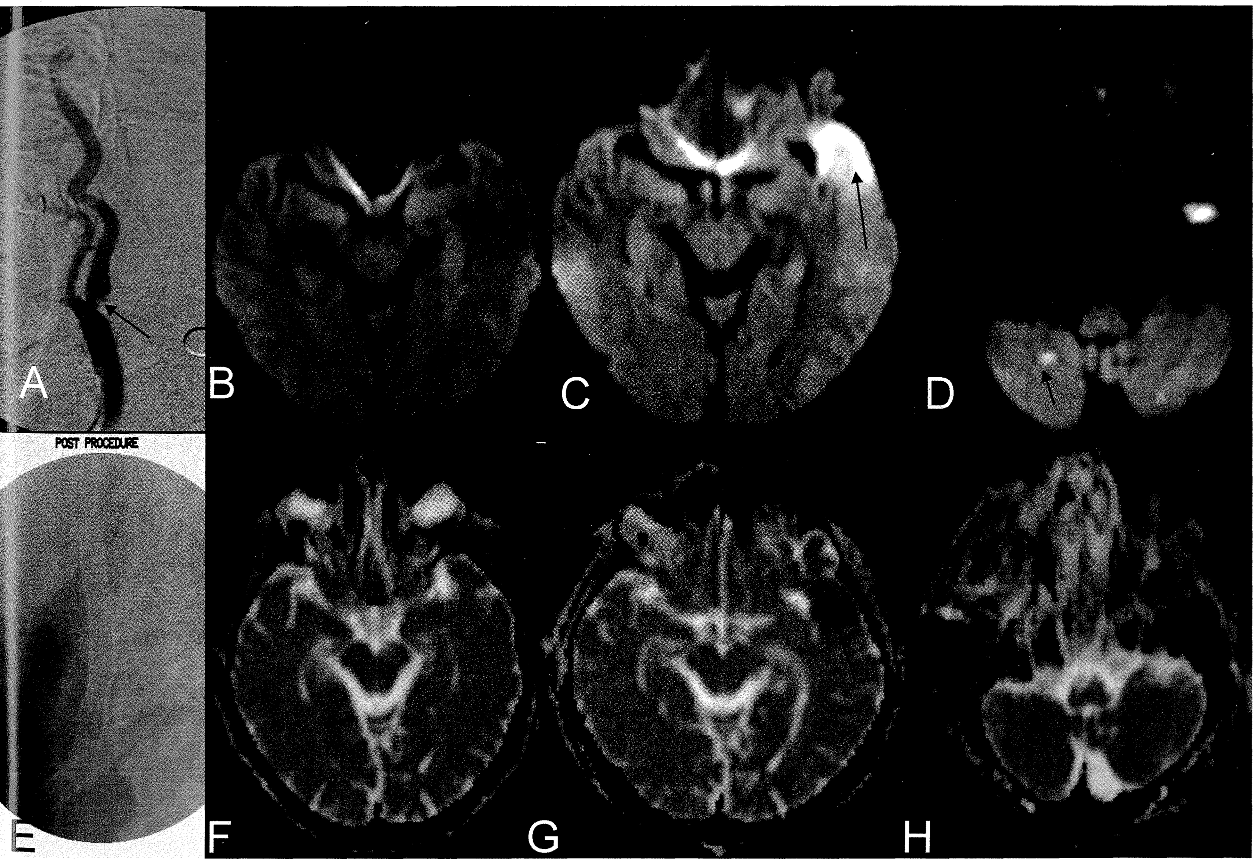
Table: 10. MTT Ratio values obtained by contralateral normal hemisphere / ipsilateral stenotic side in different territories.

	Age / Sex	ACAT 1		MCAT 1		ACAT 2		MCAT 2	
		Pre Pro	Post Pro	Pre Pro	Post Pro	Pre Pro	Post Pro	Pre Pro	Post Pro
1	65Y/ M	0.82	0.96	0.84	0.98	0.9	1	0.88	1.02
2	60Y/ M	0.84	0.98	0.88	1	0.88	1.01	0.9	1.01
3	51Y/ M	0.9	1.02	0.91	1.02	0.91	1.03	0.87	1
4	55Y/ M	0.83	0.91	0.86	0.9	0.88	1	0.91	0.92
5	66Y/ F	0.88	1.02	0.84	0.97	0.87	0.98	0.87	0.99
6	56Y/ M	0.84	0.99	0.8	0.99	0.91	0.99	0.89	0.98
7	59Y/ M	0.87	0.98	0.9	1.03	0.88	1.02	0.9	1
Mean		0.854	0.98	0.861	0.984	0.89	1.004	0.888	0.988
S.D		0.029	0.038	0.038	0.043	0.016	0.017	0.016	0.033
P value		0.0001		0.0001		0.0001		0.0001	

MTT : Mean Transit Time, ACAT : Anterior Cerebral Artery Territory, MCAT: Middle Cerebral Artery Territory, Pro : Procedure.



g 8. Patient with left ICA stenosis. A and E, FLAIR images pre and postprocedure. B and F preprocedure WI and ADC maps. C, D, G and H post procedure DWI and ADC maps. Patient was asymptomatic llowing left carotid stenting, but DWI images showed silent ischemic foci on both right and left sides (C and). These foci were not seen on postprocedure FLAIR images.



g. 9. Patient with left ICA stenosis with pre and post procedural images. A and E pre and postprocedure SA images. B and F are preprocedural DWI images with ADC map. C, G, D and H are postprocedural DWI ages with corresponding ADC maps. Note ulcerated plaque (A) in the left ICA with infarct (C and G) in e left temporal pole following procedure. Note silent ischemia in the right cerebellar hemisphere (D and H)

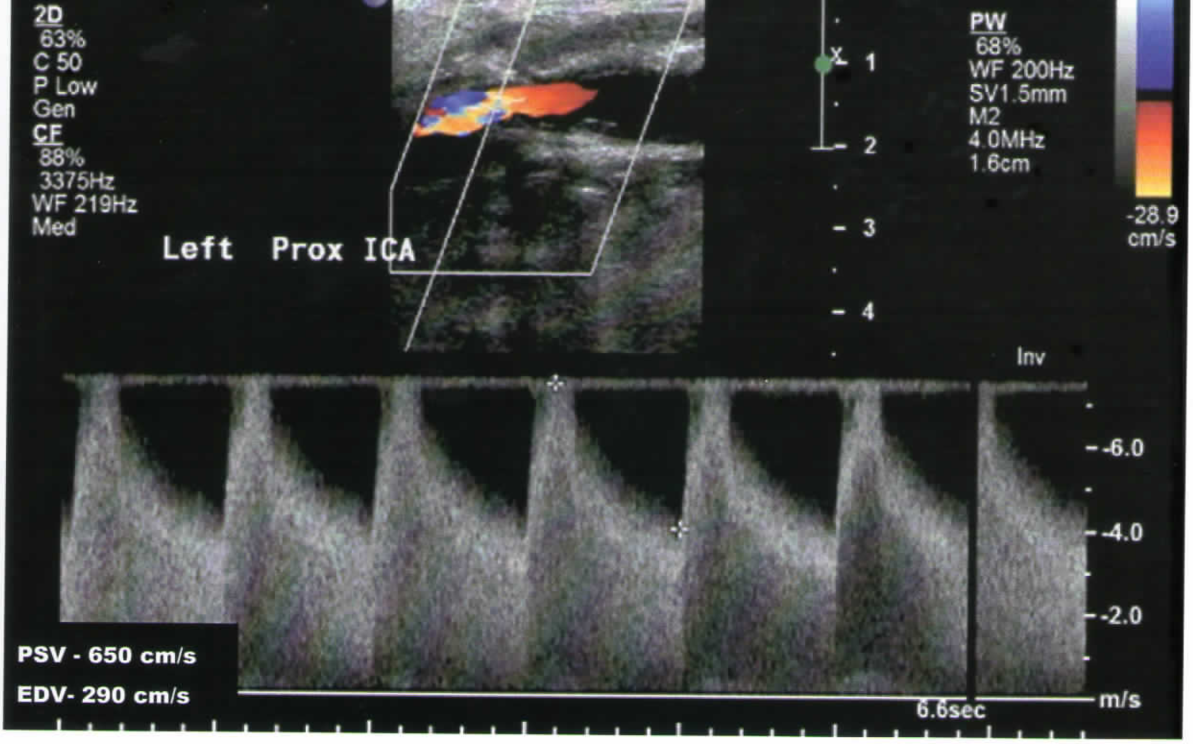


Fig: 1. Color-assisted carotid duplex ultrasonography demonstrating a severe left internal carotid artery stenosis. Note the marked elevation in peak systolic velocity (650 cm/s) and end-diastolic velocity(290 cm/s).

Fig: 2. CEMRA MIP (A and B) images of a patient with right internal carotid artery stenosis in comparison with 2D DSA (C). Note overestimation of the stenosis with CEMRA.

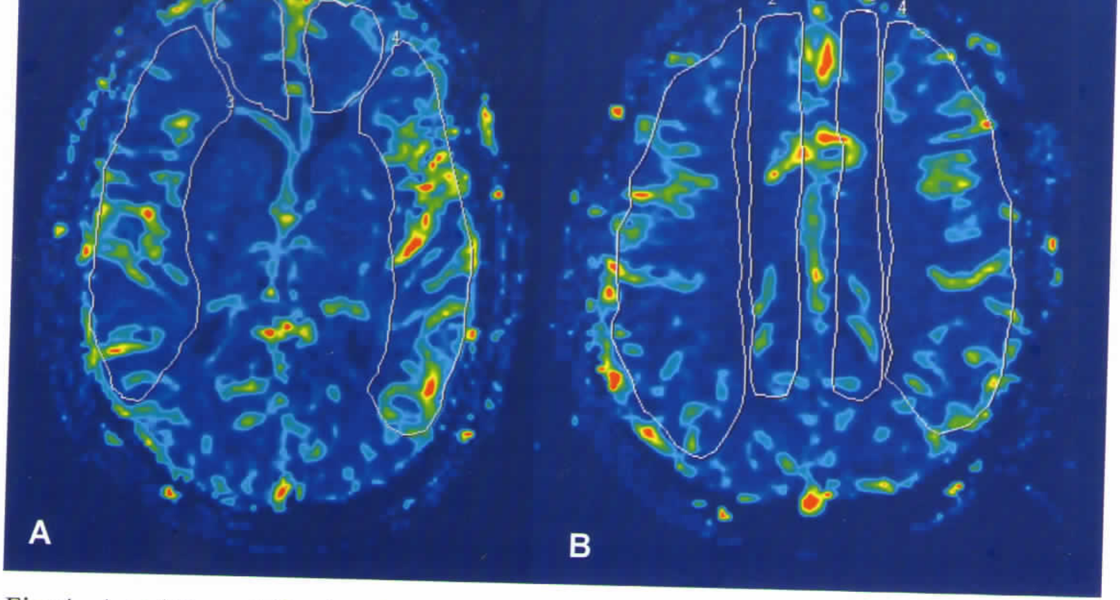


Fig: 4. A and B are defined various cerebral vascular territories at the level of basal ganglia and centrum semiovale respectively. 1, 2, 3, 4 in fig A corresponds to ACAT1, MCAT1 on right and left side. Similarly 1, 2, 3, 4 in fig B corresponds to ACAT2 and MCAT2.

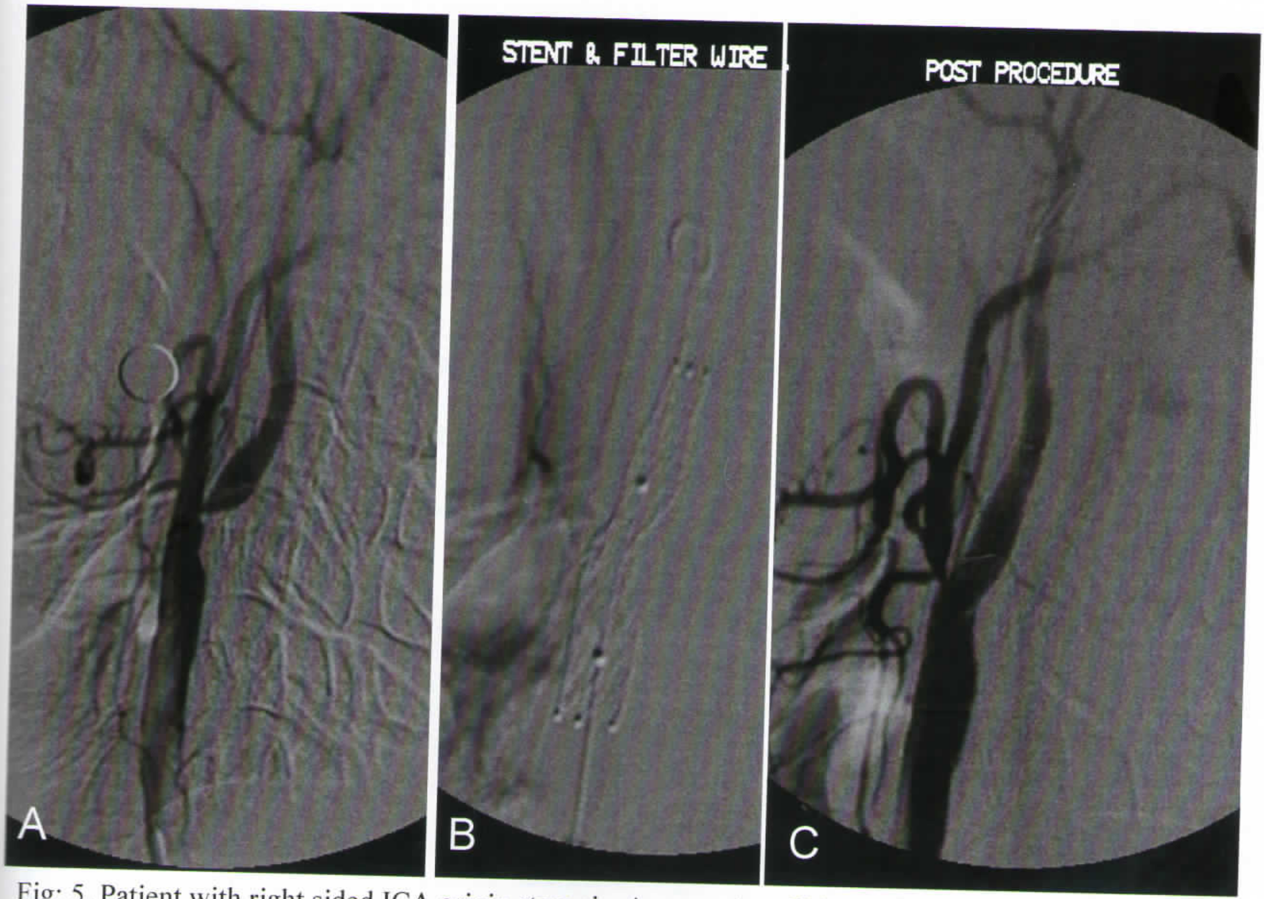


Fig: 5. Patient with right sided ICA origin stenosis. A. more than 80% stenosis. B. Lesion crossed with 0.0014'' transcend guidewire. Self expandable Stent and filter in-situ. C. Post porcedure angiographic image showing good opening of the stenosis.

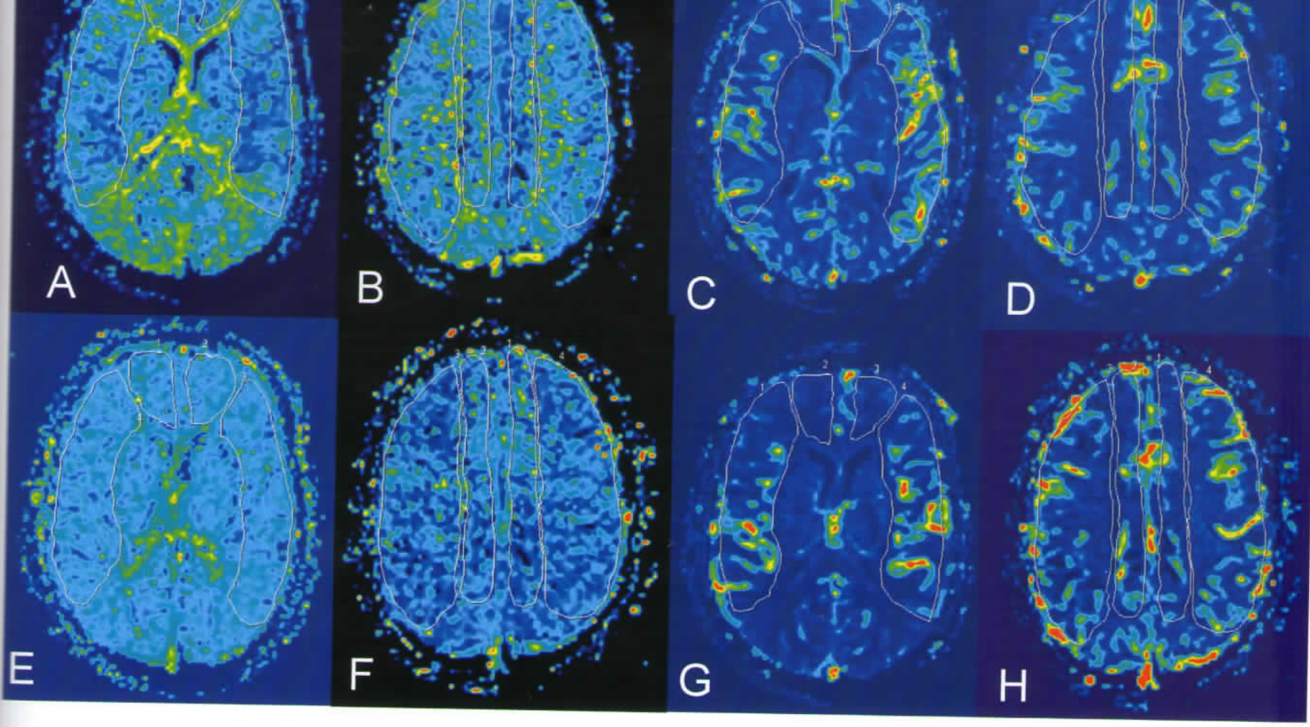


Fig: 6. Right ICA stenosis. A and B preprocedure MTT maps. C and D pre procedure CBF maps. E and F post-procedure MTT maps. G and H post procedure CBF maps. MTT was increased and CBF was decreased on right side prior to the procedure in all territories and it was normalised following stenting.

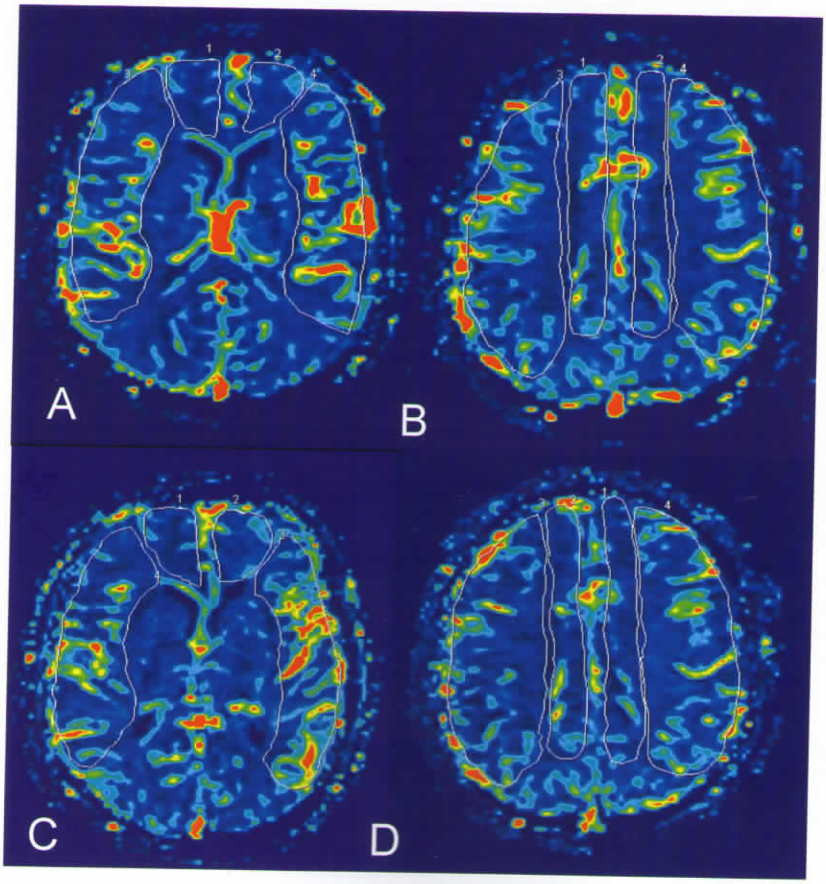


Fig.7 Right ICA stenosis. Preprocedure (A and B) and Postprocedure (C and D) CBV maps. No significant change seen in the CBV values

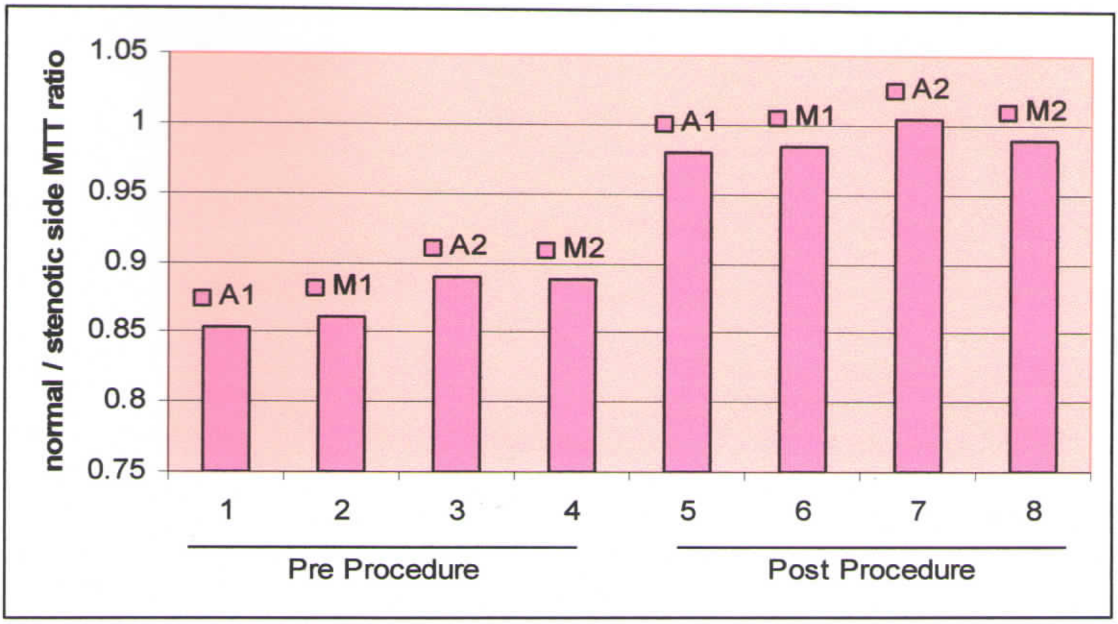


Fig 10: Differences between the pre and post procedural mean MTT (ratio) in various cerebral vascular territories. A1 and A2 – ACA territories, M1 and M2 – MCA territories.

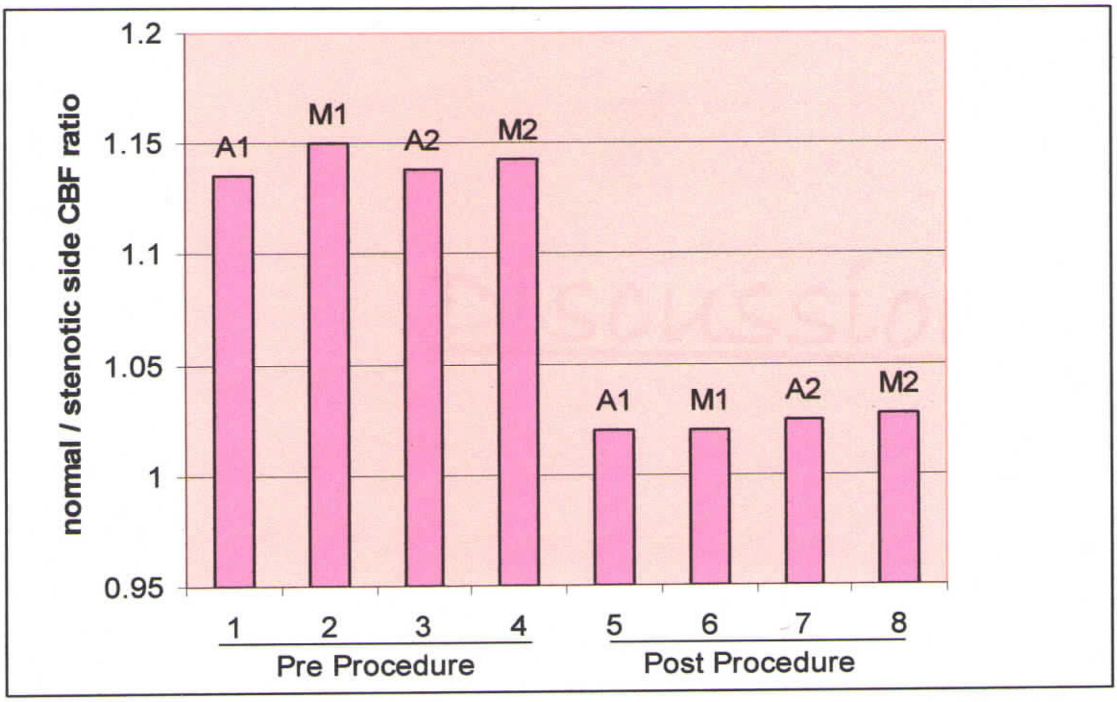


Fig 11: Differences between the pre and post procedural mean CBF (ratio) in various cerebral vascular territories. A1 and A2 – ACA territories, M1 and M2 – MCA territories.

Discussion

DISCUSSION

Patients with ICA occlusion have a variable neurologic outcome (145). The presence of ICA occlusion does not predict the hemodynamic status of the distal circulation (146). If hemodynamic factors are found to be important in the pathogenesis of ischemic stroke, then hemodynamic staging will be of the outmost importance in designing therapeutic trials. Revascularization with extracranial-intracranial bypass is reported to be more effective in patients with severely impaired cerebral hemodynamics, whereas patients with normal hemodynamics would probably benefit from antithrombotic therapy (147).

Investigators in early studies of cerebral perfusion after CEA reached conflicting conclusions (148), and improved imaging techniques have not resolved this controversy (149-152). A part of the conflicting findings can be explained by the fact that the investigators in most of these studies did not distinguish between patients with and those without a baseline perfusion deficit. Further confusion has been caused by combining data from symptomatic and asymptomatic patients, combining data on carotid occlusions and carotid stenoses, and combining data from patients with unilateral and those with bilateral disease, despite the differences in response to treatment among these various groups (149, 153-155).

In the present study no attempt was made to quantitate CBV, MTT or CBF and thus relative values were obtained and compared. Prior to stenting, we observed that there was decrease in the CBF value and increase in the MTT value in the hemisphere ipsilateral to stenosis in all the patients.

Compared to contralateral hemisphere, these values were found to be statistically significant in all the defined territories. Following the revascularization procedure, increase in the CBF and decrease in the MTT value was observed with a P value of <0.05 (Table 2 and 3). CBV values were not statistically significant between the symptomatic and asymptomatic hemisphere and also between the pre and post procedure values in all the defined territories.

Ko et al (156) observed a 21% mean increase in the ipsilateral CBF in the absence of clinical symptoms after CEA. Schroeder et al (157) found that CBF increased by a median of 37% in the ipsilateral cerebral hemisphere and 33% in the contralateral hemisphere within the first postoperative day. Ko et al (158) also observed a mean 37 +/-- 38% increase in 133Xe-CBF and a mean 19 + /-- 27% increase in relative CBF (rCBF) measured by MR perfusion immediately after stent placement in the ipsilateral hemisphere.

Wilkinson et al (11) reported that bolus transit time (TTFM), did not vary significantly between hemispheres within the ACAT or PCAT, however significant interhemispheric differences observed between MCA territories before intervention. Data obtained before and after carotid stent placement demonstrated a significant reduction in mean TTFM interhemispheric asymmetry (48% and 61% at the two MCA levels studied) within 3 hours of stent placement. Other published studies report normalization of perfusion parameters after 3 months (n=13) (159) and 2–6 months (n=19) (160). Cerebral CO2 reactivity has been shown to increase by approximately 30% after 2 days and by 50% at 2 months after PTA, to a degree similar to that observed with endarterectomy (161).

Ances et al (152) used arterial spin labeling perfusion magnetic resonance imaging (ASL-pMRI) to obtain quantifiable measurements of cerebral blood flow (CBF)(mL/100 g^{-1}/min^{-1}) and assessed CBF changes in major vascular distributions in patients (n=10) prior to and 3 months after carotid endarterectomy (CEA). No significant change in the global baseline CBF before and after CEA was observed in the group as a whole (P =.81). In patients with reduced CBF prior to CEA (<50 ml/100g/min), a significant increase in global CBF following CEA was observed. An inverse relationship existed between percent change in CBF after CEA versus baseline CBF within the anterior circulation (r =−.78, P <.05) but not in the posterior distribution (r =.25, P =.63).

Although earlier study results represented evidence of the presence of impaired perfusion in some patients with symptomatic carotid artery stenosis, it was not clear which individual patients would see a hemodynamic benefit from treatment, to what extent hemodynamic improvement could be expected, or which technique or parameter provided the most useful information. Our study results indicate that for patients with unilateral symptomatic carotid artery stenosis, the rMTT and rCBF can be used to differentiate groups of patients in whom cerebral perfusion will improve to varying extents owing to carotid artery intervention (162).

MTT has been shown to be inversely correlated with cerebral perfusion pressure (147) and according to the formula CBF = CBV/MTT, CBF is inversely related to MTT and proportional to CBV. During the first phase of hemodynamic compromise, reduced cerebral perfusion pressure results in a prolonged MTT owing to vasodilatation (163). This vasodilatation can be identified as an increase in CBV. Consequently, the CBF may remain within the normal range.

As the cerebral perfusion pressure further decreases with a concurrent increase in MTT, compensatory vasodilatation reaches a maximum and advanced hemodynamic compromise results in reduced CBF (163). Thus, the MTT may represent an early and sensitive parameter for the detection of perfusion deficits (147, 164). In our study we did not obtain a patient showing isolated increase in the MTT value, suggesting maximum haemodynamic compromise in all the included patients.

Though we did not quantitate the CBV, CBF and MTT values in our study, we believe that the main interest of our findings consist in the constant reduction in brain perfusion (decreased CBF and increased MTT) detected in the hemisphere corresponding to the stenotic carotid artery, compared with the contralateral normal hemisphere.

The neuropsychologic consequences of an ischemic event are well known, (165) though generally neglected because the attention of the physician is driven toward the more striking and invalidating motor deficits. However, recent articles have demonstrated that even asymptomatic patients with an increased ICA luminal narrowing show higher depression scores or reduced neuropsychologic test performances that seem to be reversed by CAS (141,166,167). It is, therefore, tempting, in view of these works on the neuropsychological effect of carotid stenosis, to hypothesize that the low-normal perfusion observed in our patient population, could be the cause of serious long-term effects consisting of either clinically evident depression, severely reduced attention, or memory impairment, ultimately perhaps contributing to the development of dementia(168).

New DWI focal lesions are detectable in 43% of patients (3 patients) submitted to CAS. This result is in line with previous reports that reveal a number of silent ischemic lesions after CAS ranging from 22% to 54% (169-171). The mean diameter, the subcortical location, and the prevalent distribution in the vascular territory supplied by the treated vessel of the lesions are indicative of their embolic origin; two of these patient developed neurological deficits following stenting.

Transcranial Doppler monitoring during stent implantation had clearly demonstrated that the embolization is present in most patients treated with CAS (172) and is related to guide wire, catheter manipulation, stent placement, postdilation, and balloon deflation.(173) Nevertheless, there is no relationship between the number of emboli revealed with Doppler monitoring and neurologic complications, because the majority of emboli are not particulate but include air bubbles that probably do not induce structural brain damage.(174) This could explain why no correlation was found between the total number of microembolic signals measured with transcranial Doppler during the procedure and DWI-detected lesions. (170,175) Therefore, DWI can be considered one of the most robust methods to monitor the effects of endovascular therapies.

In our study group, presence of high signal areas could be seen in both DWI and FLAIR in one patient. In other series, only a percentage of DWI lesions is visible on conventional images (171) and some of these can be reversible. Transient DWI lesions not associated with correspondent hyperintensities on FLAIR or T2 images have been reported in animals and humans; they could be attributable to acute bioenergetic compromise with early restoration of blood flow and probably are not related to brain definitive parenchymal damage.

Silent cerebral lesions after CAS have also been reported with protected devices procedures ranging from 23% to 43 %.(176,177). We can suppose that particulate plaque debris can be spread during the filter passage through the stenosis or during predilatation, when necessary, to bypass the stenosis. Moreover, we have to consider that some atherosclerotic particles may pass through the filter pores or among the filter basket. We also cannot exclude that the withdrawal of the filter protection system may squeeze captured atherosclerotic materials from the filter basket into the treated vessel.

The total number of lesions in our study group is not related exclusively to the CAS procedure, because all of the patients underwent diagnostic DSA before interventional maneuvers and emboli may source from guiding catheter placement, guide wire introduction, or retrieval before cerebral protection deployment.

Because silent cerebral lesions at DWI, after diagnostic DSA, range between 6 % (178) and 26% (179) the number of the emboli directly related to CAS is less conspicuous than that we report. Certainly, diagnostic DSA is mandatory for CAS planning, and then the global number of lesions has to be considered in the assessment of CAS safety.

A cerebral protection filter seems to reduce the number of silent ischemic lesions in patients undergoing endovascular recanalization of carotid arteries. In our series, two of the six patients (33 %) developed new DWI lesions following CAS with protection. In one patient, CAS was done without protection and had new DWI lesion. This result is in line with the assumption of an effective protective function of the filters (180).

Two of the three patients had new DWI lesions (inconsistent) contralateral to stented side. One hypothesis to explain the inconsistent lesion appearance is that emboli source from the treated vessel and proceeds through intracranial compensation supply reaching the contralateral hemisphere. This interpretation is not supported by the lack of reduction of inconsistent lesions in patients treated with cerebral protection devices. Moreover, this conflicts with the observation that the number of inconsistent lesions does not correlate with the presence of intracranial compensation circles. Finally, inconsistent DWI lesions are reported after CAS but not after CEA,(170) indicating that maneuvers on the aortic arch and unaffected vessels play a predominant role in the occurrence of inconsistent silent cerebral ischemia (176). The incidence of inconsistent silent cerebral lesions points out the need for the development of less traumatic endoluminal devices.

One of the reasons for the increased incidence of DWI hyperintense lesions in our study is the exclusive use of open cell designed stents in all our patients. Schnaudigel et al (137) indicated closed-cell stents is associated with a significantly lower incidence of new ipsilateral DWI lesions than the use of open-cell designed stents. This finding could be related to the greater potential of closed-cell stents at preventing continuous embolization attributable to further small particles breaking off the fractured plaque into the blood system and subsequently into the brain. In support of this notion, the use of stents with a closed-cell design was associated with lower periprocedural complication rates in a recent analysis of a dual-center CAS database of 701 consecutive CAS patients (138).

The clinical meaning of silent cerebral ischemia is not fully understood. A recent study reports that a definite infarction after endarterectomy correlates with the number and volume of postoperative DWI lesions (181) suggesting that a clinically evident stroke could represent the tip of the iceberg of embolic ischemic events (182). Nevertheless, the role of microembolic DWI lesions in stroke onset during revascularization and the consequential potential benefit in using cerebral protection devices is currently under judgment and will be the challenge of additional larger randomized studies.

Until now, silent brain infarcts were associated with a decline in global cognitive function (183) and particulate embolization during cardiovascular interventions or CEA seems to be correlated with neuropsychometric deterioration. Subclinical infarcts end up with cognitive deficits on neuropsychological testing after both endarterectomy and carotid artery stenting (134). Theoretically, cerebral protection could play a role in reducing the effects of microemboli on cognitive functions after endovascular procedures.

Symptomatic status of patients, as well comorbidity, is not related to the incidence of silent ischemic lesions detectable with DWI as all are symptomatic patients in our study. Cosottini et al (14) made a similar observation and found that symptomatic status of the patient, co-morbidities, radiological variables and procedural variables were not correlated with the development of new DWI lesions.

The main limitation of our work is the small cohort of patient population included in our study. There was no incidence of hyperperfusion syndrome complication in any of our patient so that conclusion of variation of perfusion parameters (both pre and immediate post procedural) in these patients cannot be drawn in our study.

Quantitative hemodynamic measurements of perfusion parameters were not possible in our study. If it is obtained before and after treatment, it may provide insight into the pathophysiologic characteristics of stroke in the setting of vascular stenoses. The severity of stenosis alone does not appear to be correlated with changes in brain perfusion in both symptomatic and asymptomatic cases. Use of perfusion data may allow more accurate assessment of stroke risk and improve selection of patients who may benefit from revascularization procedures.

The absence of neuropsychological monitoring with appropriate tests to evaluate an eventual cognitive impairment related to the embolic lesions / to decreased perfusion is a limitation for our study.

Conclusions

CONCLUSIONS

- Carotid artery stenting was found to be associated with incidences of new DWI lesion both inside and outside the treated artery territory.
- The use of distal embolic protection devices in CAS can further reduce adverse events after carotid interventions. Caution should be used concerning the efficacy of the currently available distal filter devices in view of the relatively high number of new silent ischemic lesions and the fact that filter devices in place are potentially unable to capture all the debris and, furthermore, potentially can provoke cerebral emboli.
- Incidences of new DWI lesion are high with the use of open cell design stents.
- Carotid stenosis is associated with asymmetry in interhemispheric perfusion with mild decrease in the cerebral blood flow and increase in the circulation time.
- MR perfusion, as assessed by using an exogenous contrast agent, is a reasonable alternative for detecting asymmetry in hemispheric perfusion. It also appears to be a marker for the cerebral hemodynamic sequelae of intervention in carotid disease.

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Abbreviations

ABBREVIATIONS

- ACA – Anterior Cerebral Artery.
- ACAT -- Anterior Cerebral Artery Territory.
- ALN – Artificial Luminal Narrowing.
- ASL-pMRI – Arterial Spin Labeling, Perfusion Magnetic Resonance Imaging.
- CARESS – Carotid Revascularization Using Endarterectomy Or Stenting Systems.
- CAS – Carotid Artery Stenting.
- CAVATAS – Carotid and Vertebral Artery Transluminal Angioplasty Study.
- CAVATAS-MED -- Carotid and Vertebral Artery Transluminal Angioplasty Study- Medicine.
- CBF --- Cerebral Blood Flow.
- CCA -- Common Carotid Artery.
- CDUS – Colour Doppler Ultrasonography.
- CEA --- Carotid Endarterectomy.
- CE-MRA – Contrast Enhanced Magnetic Resonance Angiography.
- CT – Computed Tomography.
- CTA – Computed Tomography Angiography.
- CVA – Cerebro Vascular Accident.
- DSA --- Digital Subtraction Angiography.
- DUS – Doppler Ultrasonography.
- DWI – Diffusion Weighted Imaging.

- ECST – European Carotid Surgery Trials.
- EDV – End Diastolic Velocity.
- EVA-3S – Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis.
- FLAIR – Fluid Attenuation Inversion Recovery.
- FOV – Field Of View.
- ICA – Internal Carotid Artery.
- MCA – Middle Cerebral Artery.
- MCAT -- Middle Cerebral Artery Territory.
- MDCT – Multi Detector Computed Tomography
- MOTSA – Multiple Thin Slab Acquisition.
- MRA – Magnetic Resonance Angiography.
- MRI – Magnetic Resonance Imaging.
- MTT – Mean Transit Time.
- NASCET – North American Symptomatic Carotid Endarterectomy Trial.
- PCA – Posterior Cerebral Artery.
- PCT – Perfusion Computed Tomography.
- PET – Positron Emission Tomography.
- PSV – Peak Systolic Velocity.
- PTA – Percutaneous Transluminal Angioplasty.
- PWI – Perfusion Weighted Imaging.
- rCBF – Relative Cerebral Blood Flow.
- rCBV -- Relative Cerebral Blood Volume.

- rMTT -- Relative Mean Transit Time.
- ROI – Region of Interest.
- SAPPHIRE – Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy.
- SPACE – Stent Supported Percutaneous Angioplasty Of The Carotid Artery Versus Endarterectomy.
- SPECT – Single Photon Emission Computed Tomography.
- TIA – Transient Ischemic Attacks.
- TOF – Time of Flight.
- TOF-MRA -- Time of Flight – Magnetic Resonance Angiography.
- TR/TE/TI – Repitition Time / Time of Echo / Time of Inversion.
- TTFM – Transit Time First Moment (Bolus Transit Time).
- Xe-CT – Xenon Computed Tomography.

Proforma

DEPARTMENT OF IMAGING SCIENCES AND INTERVENTIONAL RADIOLOGY

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PROFORMA FOR CAROTID STENTING AND PRE AND POST PROCEDURE MRI EVALUATION WITH PERFUSION AND DIFFUSION WEIGHTED IMAGES

I) PATIENT DETAILS

Name:

Age/Sex: Hospital No:

DOA: DOD: D/O PROCEDURE:

Occupation:

Address:

Phone:

E-Mail:

II) PRESENTING COMPLAINTS:

a) Neurological deficits:

b) TIA's (sensory / motor / ocular):

c) Transient loss of vision (Amaurosis Fugax)

d) Bowel and bladder involvementHeadache:

e) Seizures:

f) LOC / Altered sensorium:

B. Personal history:

HT / DM / MI / CAD / Stroke:

Br Asthma / TB:

History of Allergies:

Smoking / Alcohol:

H/o prior hospitalization:

C. Family History:

Similar medical illness in family members:

D. Prior treatment history:

III) EXAMINATION:

A. GENERAL EXAMINATION:

Cutaneous stigmata: carotid thrill

Carotid bruit : unilateral / bilateral

B. NEUROLOGICAL EXAMINATION:

Higher mental functions (speech):

Cranial nerve deficits:

Motor deficits:

Sensory deficits:

Meningeal signs:

Cerebellar signs:

C. OTHER SYSTEM EXAMINATION :

Respiratory system:

Cardiovascular system:

Per abdomen:

IV) INVESTIGATIONS:

Hb:	TC/DC:
ESR:	Platelets:
PT :	aPTT:
Bl Urea:	Sr. Creatinine:
LFT:	Lipid Profile:
Bl. Group:	HIV:
HBs Ag:	HCV:
VDRL:	RBS / FBS:
Others:	

V) IMAGING:

A. Carotid Doppler Study :

Date /Findings: degree of stenosis. Unilateral / Bilateral. Plaque morphology

B. CT Angiography:

Date /Findings:

C. MR Brain:

Preprocedure: Date /Findings

T1WI / T2WI / FLAIR.

CEMRA : Degree of stenosis.

DWI : Foci of restricted / facilitated diffusion – territory of involvement.

PWI : Ratio of Values : contralateral / ipsilateral sides.

	ACAT1	ACAT2	MCAT1	MCAT2
CBV				
CBF				
MTT				

Postprocedure: Date /Findings

T1WI / T2WI / FLAIR.

CEMRA in any.

DWI : Foci of restricted / facilitated diffusion – territory of involvement.

PWI : Ratio of Values : contralateral / ipsilateral sides.

	ACAT1	ACAT2	MCAT1	MCAT2
CBV				
CBF				
MTT				

D. USG Abdomen:

Date/Findings:

E. Angiogram:

a) Date:

b) Access site:

CFA Right /Left / Bilateral Other Sites

c) Side of stenosis:

d) Grade of the stenosis (NASCET Criteria):

e) Ulcerated plaque (yes / no):

f) Tandem lesions:

g) Contralateral ICA stenosis :

h) Stenosis involving CCA / Vertebral arteries :

i) Cross circulation: Satisfactory / Unsatisfactory

j) Patency of ACom / PCom :

k) Associated aneurysms / Avm's :

l) Other vascular anomalies / variations:

VII) MANAGEMENT

A) ANAESTHESIA: LA / STAND BY

B) PROCEDURE DONE:

Stenting of the carotid stenosis :

Time Taken:

a) Material used:

b) Types of stent:

c) Balloon used for dilatation:

d) Filter used:

e) Guiding catheter:

f) Guidewire:

g) Microcatheter / Microwire:

h) Others:

VIII) CHECK ANGIOGRAM:

Residual stenosis:

Distal occlusion of vessels:

IX) INTRA PROCEDURAL COMPLICATION & MANAGEMENT:

X) **Post procedural neurological status:**

Post procedural medications:

Details of ICU stay:

XI) FOLLOW UP CAROTID DOPPLER STUDY

XII) ADDITIONAL COMMENTS:

XIII) PERFORMING RADIOLOGIST:

ASSISTANT **CONSULTANT**